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(71) Applicant (for all designated States except US): **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **DUPLANTIER, Allen, Jacob** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).

(74) Agents: **LUMB, Trevor, J.** et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

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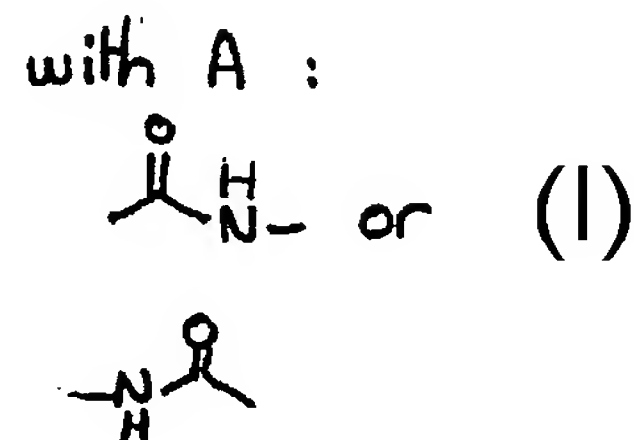
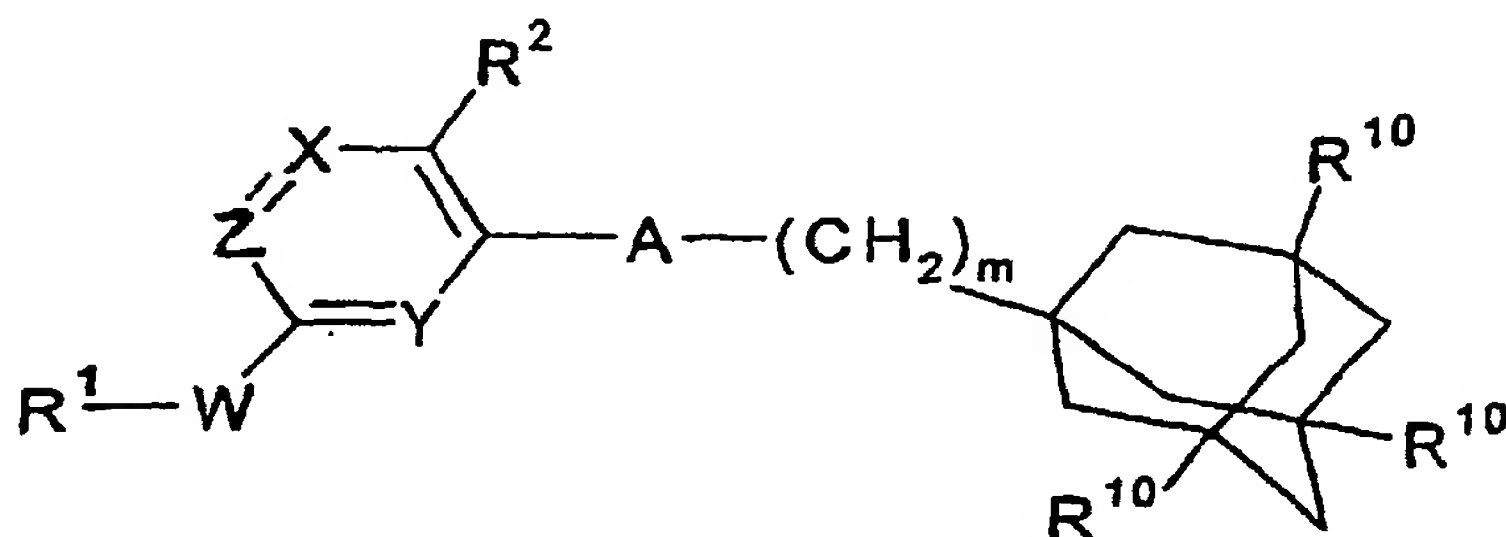
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(54) Title: N-ALKYL-ADAMANTYL DERIVATIVES AS P2X7-RECEPTOR ANTAGONISTS



(57) Abstract: The present invention relates to novel to N-alkyl adamantyl triazinyl benzylamide derivatives of formula (I) and to process for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them, and their use in the treatment of inflammation, osteoarthritis, rheumatoid arthritis, cancer, reperfusion or ischemia in stroke or heart attack, autoimmune diseases and other disorders.

WO 03/042190 A1

N-ADAMANTYLALKYL BENZAMIDE DERIVATIVES AS P2X<sub>7</sub>-RECEPTOR ANTAGONISTS

The present invention relates to N-alkyl adamantyl triazinyl benzamide derivatives, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them, and their use in therapy. The active compounds of the present invention are useful in the treatment of inflammatory diseases such as osteoarthritis and rheumatoid arthritis; allergies, asthma, COPD, cancer, reperfusion or ischemia in stroke or heart attack, autoimmune diseases and other disorders. The active compounds are also antagonists of the P2X<sub>7</sub> receptor.

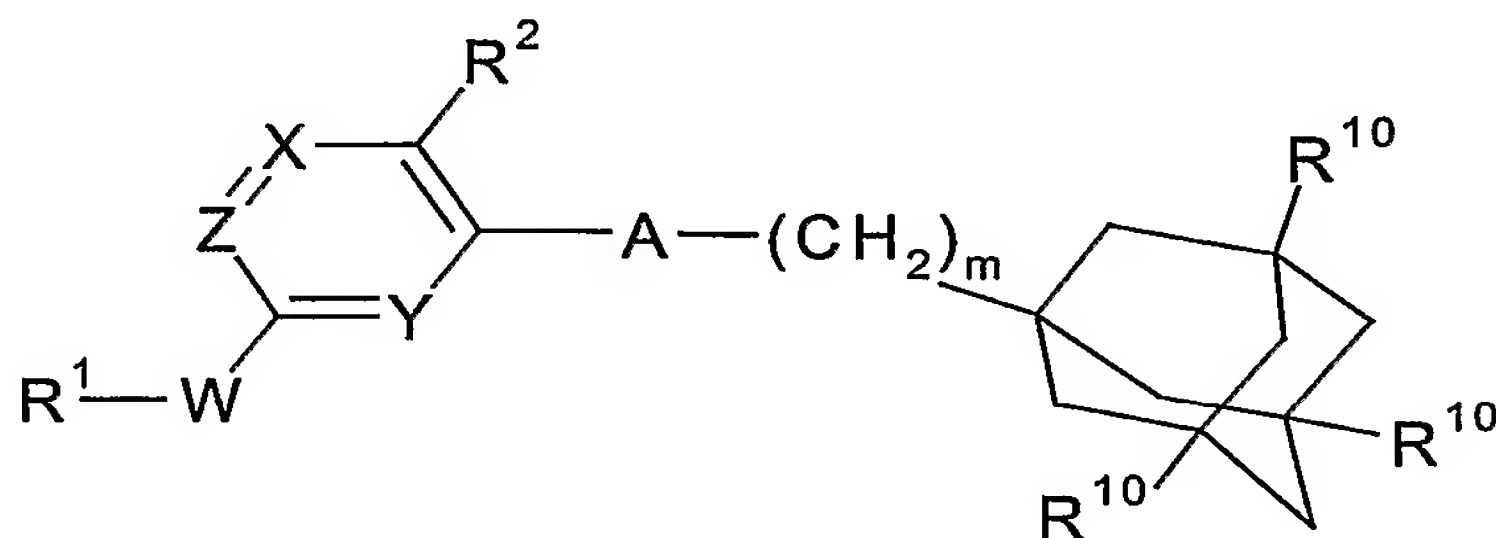
The P2X<sub>7</sub> receptor (previously known as P2Z receptor), which is ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X<sub>7</sub> receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1 $\beta$  (IL-1 $\beta$ ) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and proliferation (T cells), apoptosis and L-selectin shedding (lymphocytes). P2X<sub>7</sub> receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes and mesangial cells.

P2X<sub>7</sub> antagonists are known in the art, such as International Patent Publications WO 01/46200, WO 01/42194, WO 01/44213, WO99/29660, WO 00/61569, WO 99/29661, WO 99/29686, WO 00/71529, and WO 01/44170.

Benzamides, heteroarylamides and reverse amides for uses other than inhibition of P2X<sub>7</sub> have been published, such as International Patent Publications WO 97/22600, EP 138,527, WO 00/71509, WO 98/28269, WO 99/17777 and WO 01/58883.

**SUMMARY OF THE INVENTION**

The present invention relates to a compound of the formula



wherein A is  $-(C=O)NH-$  or  $-NH(C=O)-$ ; preferably  $-(C=O)NH-$ ;

X, Y and Z are  $=(CR^3)-$ ,  $=(CR^4)-$ , and  $=(CR^5)-$ ; or  $=N-$ ,  $=(CR^4)-$ , and  $=(CR^5)-$ ; or  $=(CR^3)-$ ,  $=N-$ , and  $=(CR^5)-$ ; or  $=(CR^3)-$ ,  $=(CR^4)-$ , and  $=N-$ ; or  $=N-$ ,  $=(CR^4)-$ , and  $=N-$ ; or  $=(CR^3)-$ ,  $=N-$ , and  $=N-$ ; or  $=N-$ ,  $=N-$ , and  $CR^5$ , respectively;

W is a bond,  $-O-$ ,  $>(C=O)$ ,  $-(CH_2)_o-$ ,  $-(CH=CH)-$ ,  $-C\equiv C-$ ,  $-(CH_2)_oO-$ ,  $-O(CH_2)_o-$ ,  $-O(CH_2)_pO-$ ,  $-O(CH_2)_qO(CH_2)_r-$ ,  $-CR^6(OH)-$ ,  $-(CH_2)_rO(CH_2)_r-$ ,  $-(CH_2)_rO(CH_2)_qO$ ,  $>NR^7$ ,

$-(CH_2)_oNR^7-$ ,  $-NR^7(CH_2)_o-$ ,  $-(CH_2)_rNR^7(CH_2)_r-$ ,  $-O(CH_2)_pNR^7-$ ,  $-O(CH_2)_qNR^7(CH_2)_r-$ ,  
 $-(CH_2)_rNR^7(CH_2)_qO-$ ,  $-NR^7(CH_2)_qO-$ ,  $-NR^7(CH_2)_qO(CH_2)_r-$ ,  $-CONR^7-$ ,  $-NR^7CO-$ ,  $>S(O)_n$ ,  
 $-S(O)_nCH_2-$ ,  $-CH_2S(O)_n-$ ,  $-SO_2NR^7-$ , or  $-NR^7SO_2-$ ;

m is an integer from 1 to 2;

5 n is an integer from 0 to 2;

o is an integer from 1 to 6;

p is an integer from 2 to 6;

q is an integer from 2 to 3;

r is an integer from 1 to 3;

10  $R^1$  is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring containing three to five nitrogen atoms and zero to three additional heteroatoms independently selected from the group consisting of  $-O-$  and  $S(O)_n$ ; wherein any of said carbon atoms of said 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring may optionally contain 1-3 oxo groups; wherein one to three of said nitrogen  
 15 atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring;

$R^2$  is selected from the group of suitable substituents such as (i) hydrogen, (ii) halogen, (iii) cyano, (iv)  $(C_1-C_4)$ alkyl optionally substituted by one to four chloro or fluoro, (v)  
 20  $(C_2-C_4)$ alkenyl; (vi)  $(C_2-C_4)$ alkynyl and (vii)  $(C_1-C_4)$ alkyloxy optionally substituted by one to four chloro or fluoro;

$R^3$ ,  $R^4$  and  $R^5$  are each independently selected from the group suitable substituents such as (i) hydrogen; (ii) halogen, (iii) cyano, (iv) nitro, (v) amino, (vi) hydroxyl, (vii)  $(C_1-C_6)$ alkyl optionally substituted by one to four chloro or fluoro, (viii)  $(C_3-C_8)$ cycloalkyl  
 25 optionally substituted by one to four chloro or fluoro, (ix)  $(C_1-C_6)$ alkyloxy optionally substituted by one to four chloro or fluoro, and (x)  $(C_3-C_8)$ cycloalkyloxy optionally substituted by one to four chloro or fluoro;

$R^6$  is hydrogen or  $(C_1-C_6)$ alkyl, preferably methyl;

$R^7$  is hydrogen,  $(C_1-C_6)$ alkyl or  $(C_3-C_8)$ cycloalkyl;

30  $R^8$  is absent or is selected from the group suitable substituents such as hydrogen,  $(C_1-C_6)$ alkyl optionally substituted with one to six fluoro,  $HO-(C_2-C_6)$ alkyl and  $(C_3-C_8)$ cycloalkyl;

$R^9$  is selected from the group suitable substituents such as hydrogen, halo,  $(C_1-C_6)$ alkyl optionally substituted with one to six fluoro,  $-CO_2H$ ,  $HO-(C_2-C_6)$ alkyl,  
 35  $(C_1-C_6)$ alkoxy optionally substituted with one to six fluoro, hydroxy,  $(C_1-C_{10})$ heteroaryl and  $(C_3-C_8)$ cycloalkyl;

each  $R^{10}$  is independently selected from the group consisting of hydrogen or halo;

or the pharmaceutically acceptable salts or solvates or prodrugs thereof.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

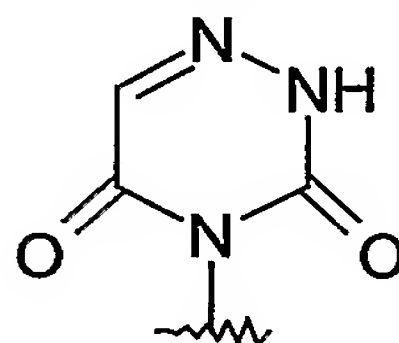
The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemossine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

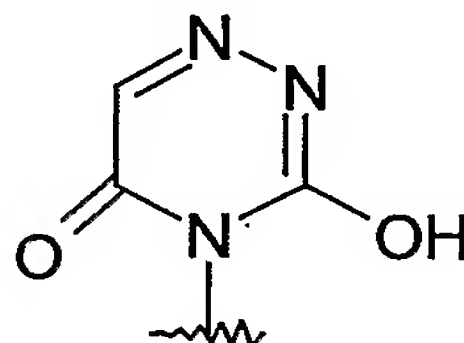
This invention also encompasses compounds of formula I containing protective groups. One skilled in the art will also appreciate that compounds of the invention can also be prepared with certain protecting groups that are useful for purification or storage and can be removed before administration to a patient. The protection and deprotection of functional groups is described in "Protective Groups in Organic Chemistry", edited by J.W.F. McOmie, Plenum Press (1973) and "Protective Groups in Organic Synthesis", 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of this invention include all stereoisomers (e.g., cis and trans isomers) and all optical isomers of compounds of the formula I (e.g., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

The compounds, salts and prodrugs of the present invention can exist in several  
5 tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds. One  
10 example of a tautomeric structure is when R<sup>1</sup> is a group of the formula



One skilled in the art will appreciate that this group can also be drawn as its tautomer



The present invention also includes atropisomers of the present invention.  
15 Atropisomers refer to compounds of formula I that can be separated into rotationally restricted isomers.

The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

20 A "suitable substituent" is intended to mean a chemically and pharmaceutically acceptable functional group i.e., a moiety that does not negate the inhibitory activity of the inventive compounds. Such suitable substituents may be routinely selected by those skilled in the art. Illustrative examples of suitable substituents include, but are not limited to halo groups, perfluoroalkyl groups, perfluoroalkoxy groups, alkyl groups, alkenyl groups, alkynyl groups,  
25 hydroxy groups, oxo groups, mercapto groups, alkylthio groups, alkoxy groups, aryl or heteroaryl groups, aryloxy or heteroaryloxy groups, aralkyl or heteroaralkyl groups, aralkoxy or heteroaralkoxy groups, HO-(C=O)- groups, amino groups, alkyl- and dialkylamino groups, carbamoyl groups, alkylcarbonyl groups, alkoxycarbonyl groups, alkylaminocarbonyl groups, dialkylamino carbonyl groups, arylcarbonyl groups, aryloxycarbonyl groups, alkylsulfonyl



groups, arylsulfonyl groups and the like. Those skilled in the art will appreciate that many substituents can be substituted by additional substituents.

As used herein, the term "alkyl," as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched (such as methyl, ethyl, *n*-propyl, *isopropyl*,  
5 *n*-butyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl); optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl. The phrase "each of said alkyl" as used herein refers to any of the preceding alkyl moieties within a group such alkoxy, alkenyl or alkylamino. Preferred alkyls include (C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably methyl and ethyl.

10 As used herein, the term "cycloalkyl" refers to a mono, bicyclic or tricyclic carbocyclic ring (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1 or 2 double bonds and optionally substituted  
15 (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl.

As used herein, the term "halogen" includes fluoro, chloro, bromo or iodo or fluoride, chloride, bromide or iodide.

As used herein, the term "halo-substituted alkyl" refers to an alkyl radical as described above substituted with one or more halogens included, but not limited to,  
20 chloromethyl, dichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trichloroethyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl.

As used herein, the term "alkenyl" means straight or branched chain unsaturated  
25 radicals of 2 to 6 carbon atoms, including, but not limited to ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl.

As used herein, the term "(C<sub>2</sub>-C<sub>6</sub>)alkynyl" is used herein to mean straight or branched  
30 hydrocarbon chain radicals having one triple bond including, but not limited to, ethynyl, propynyl, butynyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl.

As used herein, the term "carbonyl" or "(C=O)" (as used in phrases such as  
35 alkylcarbonyl, alkyl-(C=O)- or alkoxycarbonyl) refers to the joiner of the >C=O moiety to a second moiety such as an alkyl or amino group (i.e. an amido group). Alkoxycarbonylamino (i.e. alkoxy(C=O)-NH-) refers to an alkyl carbamate group. The carbonyl group is also

equivalently defined herein as (C=O). Alkylcarbonylamino refers to groups such as acetamide.

As used herein, the term "aryl" means aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like; optionally substituted by 1 to 3 suitable substituents as  
5 defined above such as fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl.

As used herein, the term "5 to 10 membered saturated heterocyclic ring" refers to a cyclic group containing 1-7 carbon atoms containing three to five nitrogen heteroatoms and zero to three additional heteroatoms independently selected from the group consisting of -O-  
10 and -S(O)<sub>n</sub>- and each of the bonds between ring members is a single bond and wherein said ring is optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl. Examples of such rings include 1,2,3-triazolidine, 1,2,4-triazolidine, tetrazolidine, 1,2,3,4-oxatriazolidine, 1,2,3,5-oxatriazolidine, perhydro-1,2,3-triazine,  
15 perhydro-1,3,5-triazine, perhydro-1,2,4-triazine, perhydro-purine, perhydro-pyrazolopyridine, perhydro-triazolopyridine, dihydro-6-azauracil, perhydro-pteridine, 1,2,3,4-thiatrizolidine and 1,2,3,5-thiatrizolidine.

As used herein, the term "5 to 10 membered unsaturated heterocyclic ring" refers to a cyclic group containing 1-7 carbon atoms containing three to five nitrogen heteroatoms and  
20 zero to three additional heteroatoms independently selected from the group consisting of -O- and -S(O)<sub>n</sub>- and at least two of the bonds between ring members are double bonds such that the ring is an aromatic ring. Examples of such rings include 1,2,3-triazole, 1,2,4-triazole, 1-H-pyrazolo[4,3-d]oxazole, 4H-imidazo[4,5-d]thiazole, imidazo[1,2-b][1,2,4]triazine, tetrazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-triazine, 1,3,5-triazine, 1,2,4-triazine, purine,  
25 pyrazolopyridine, pyrazino[2,3-d]pyridazine, triazolopyridine, xanthine, pteridine, 1,2,3,4-thiatrizole and 1,2,3,5-thiatrizole.

As used herein, the term "5 to 10 membered partially unsaturated heterocyclic ring" refers to a cyclic group containing 1-7 carbon atoms containing three to five nitrogen heteroatoms and zero to three additional heteroatoms independently selected from the group  
30 consisting of -O- and -S(O)<sub>n</sub>- and at least one of the bonds between ring members is a double bond. Examples of such rings include dihydro-1,2,3-triazole, dihydro-1,2,4-triazole, dihydro-tetrazole, dihydro-1,2,3,4-oxatriazole, dihydro-1,2,3,5-oxatriazole, dihydro-1,2,3-triazine, dihydro-1,3,5-triazine, dihydro-1,2,4-triazine, dihydro-purine, dihydro-pyrazolopyridine, dihydro-triazolopyridine, 7,9-dihydro-3H-purine-2,6,8-trione,  
35 6-azauracil, xanthine, dihydro-pteridine, dihydro-1,2,3,4-thiatrizole and dihydro-1,2,3,5-thiatrizole. Preferred R<sup>1</sup> heterocycles include 6-azauracil.

As used herein, the term "heteroaryl" refers to an aromatic heterocyclic group usually with one heteroatom selected from O, S and N in the ring. In addition to said heteroatom, the aromatic group may optionally have up to four N atoms in the ring. For example, heteroaryl group includes pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), quinolyl, isoquinolyl, benzothienyl, benzofuryl, indolyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy or (C<sub>1</sub>-C<sub>6</sub>)alkyl. Particularly preferred heteroaryl groups include oxazolyl, imidazolyl, pyridyl, thienyl, furyl, thiazolyl and pyrazolyl.

Nitrogen heteroatoms as used herein refers to N=, >N and -NH; wherein N= refers to a nitrogen double bond connection; >N refers to a nitrogen containing two bond connections and -N refers to a nitrogen containing one bond connection.

"Embodiment" as used herein refers to specific groupings of compounds or uses into discrete subgenera. Such subgenera may be cognizable according to one particular substituent such as a specific R<sup>1</sup> or R<sup>2</sup> group. Other subgenera are cognizable according to combinations of various substituents, such as all compounds wherein R<sup>2</sup> is chloro and R<sup>1</sup> is optionally substituted 6-azauracil. The phrase "in combination with each of the aforementioned embodiments" refers to combinations of the identified embodiment with each embodiment previously identified in the specification. Thus an embodiment of compounds wherein R<sup>1</sup> is optionally substituted 6-azauracil "in combination with each of the aforementioned embodiments" refers to additional embodiments comprising combinations of the R<sup>1</sup> optionally substituted 6-azauracil embodiment with each embodiment previously identified in the specification.

A preferred embodiment of the present invention, referred to as the phenyl compounds, are those compounds of formula I wherein X, Y and Z are =(CR<sup>3</sup>)-, =(CR<sup>4</sup>)-, and =(CR<sup>5</sup>)-.

An embodiment of the present invention, referred to as the pyridyl compounds, are those compounds of formula I wherein =N-, =(CR<sup>4</sup>)-, and =(CR<sup>5</sup>)-.

Another embodiment of the present invention, referred to as the pyridyl compounds, are those compounds of formula I wherein =(CR<sup>3</sup>)-, =N-, and =(CR<sup>5</sup>)-.

Another embodiment of the present invention, referred to as the pyridyl compounds, are those compounds of formula I wherein =(CR<sup>3</sup>)-, =(CR<sup>4</sup>)-, and =N-.

Another embodiment of the present invention, referred to as the pyridazine compounds, are those compounds of formula I wherein =N-, =(CR<sup>4</sup>)-, and =N-.



Another embodiment of the present invention, referred to as the pyrimidine compounds, are those compounds of formula I wherein  $=(\text{CR}^3)-$ ,  $=\text{N}-$ , and  $=\text{N}-$ .

Another embodiment of the present invention, referred to as the pyrazine compounds, are those compounds of formula I wherein  $=\text{N}-$ ,  $=\text{N}-$ , and  $\text{CR}^5$ .

5 Another embodiment of the present invention are those compounds of formula I wherein one of  $\text{R}^3$ ,  $\text{R}^4$  or  $\text{R}^5$  is selected from the group consisting of (i) hydrogen (ii) halogen, (ii) cyano, (iii) nitro, (iv) amino, (v) hydroxyl, (vi)  $(\text{C}_1-\text{C}_6)$ alkyl optionally substituted by one to four chloro or fluoro, (vii)  $(\text{C}_3-\text{C}_8)$ cycloalkyl optionally substituted by one to four chloro or fluoro, (viii)  $(\text{C}_1-\text{C}_6)$ alkyloxy optionally substituted by one to four chloro or fluoro, and (ix)  
10  $(\text{C}_3-\text{C}_8)$ cycloalkyloxy optionally substituted by one to four chloro or fluoro. A more preferred embodiment of the invention are those compounds of formula I wherein one of  $\text{R}^3$ ,  $\text{R}^4$  or  $\text{R}^5$  is selected from the group consisting of hydrogen, halogen, cyano, hydroxyl,  $(\text{C}_1-\text{C}_4)$ alkyl optionally substituted by one to four chloro or fluoro, and  $(\text{C}_1-\text{C}_4)$ alkyloxy optionally substituted by one to four chloro or fluoro. An even more preferred embodiment of the invention are  
15 those compounds of formula I wherein one of  $\text{R}^3$ ,  $\text{R}^4$  or  $\text{R}^5$  is selected from the group consisting of hydrogen, fluoro, cyano, methyl,  $-\text{CF}_3$ , methoxy and  $-\text{OCF}_3$ . Most preferably each of  $\text{R}^3$ ,  $\text{R}^4$  or  $\text{R}^5$  is hydrogen.

Another embodiment of the present invention are those compounds of formula I wherein m is one.

20 A preferred embodiment of the present invention, referred to as the amide compounds or more specifically as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, and pyrazinamide compounds, are those compounds of formula I wherein A is  $-(\text{C}=\text{O})\text{NH}-$ .

Another embodiment of the present invention, referred to as the reverse amide  
25 compounds or more specifically as the formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds, are those compounds of formula I wherein A is  $-\text{NH}(\text{C}=\text{O})-$ .

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine,  
30 carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $\text{R}^1$  is a 5 membered saturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $\text{R}^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $\text{R}^9$   
35 substituents per ring; more preferably wherein  $\text{R}^8$  and  $\text{R}^9$  are each independently hydrogen or  $(\text{C}_1-\text{C}_6)$ alkyl, more preferably hydrogen or  $(\text{C}_1-\text{C}_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 5 membered unsaturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 5 membered partially unsaturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 6 membered saturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 6 membered unsaturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent

may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

5 Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 6  
10 membered partially unsaturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more  
15 preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 7  
20 membered monocyclic saturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each  
25 independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 7  
30 membered monocyclic unsaturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each  
35 independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 7  
5 membered monocyclic partially unsaturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each  
10 independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 7  
15 membered bicyclic saturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each  
20 independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 7  
25 membered bicyclic unsaturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each  
30 independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 7  
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membered bicyclic partially unsaturated heterocyclic ring containing three to four nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted  
5 by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine,  
10 carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 8 membered monocyclic saturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said  
15 heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 8  
20 membered monocyclic unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said  
25 heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 8  
30 membered monocyclic partially unsaturated heterocyclic ring containing three to five nitrogen  
35 atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted

by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 8 membered bicyclic saturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 8 membered bicyclic unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 8 membered bicyclic partially unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 9  
5 membered monocyclic saturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each  
10 independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 9  
15 membered monocyclic unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each  
20 independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 9  
25 membered monocyclic partially unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted  
30 by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 9  
35

membered bicyclic saturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 9 membered bicyclic unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 9 membered bicyclic partially unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 10 membered monocyclic saturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by



one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 10 membered monocyclic unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

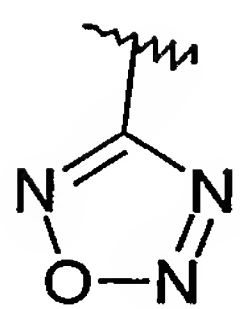
Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 10 membered monocyclic partially unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is a 10 membered bicyclic saturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring; more preferably wherein  $R^8$  and  $R^9$  are each independently hydrogen or  $(C_1-C_6)$ alkyl, more preferably hydrogen or  $(C_1-C_4)$ alkyl, more preferably hydrogen or methyl.

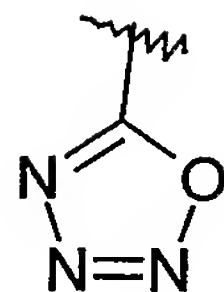
Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 10 membered bicyclic unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is a 10 membered bicyclic partially unsaturated heterocyclic ring containing three to five nitrogen atoms; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by R<sup>8</sup>; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four R<sup>9</sup> substituents per ring; more preferably wherein R<sup>8</sup> and R<sup>9</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, more preferably hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydrogen or methyl.

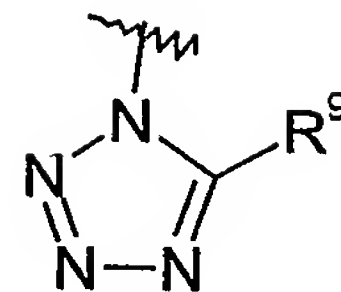
Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is selected from the group



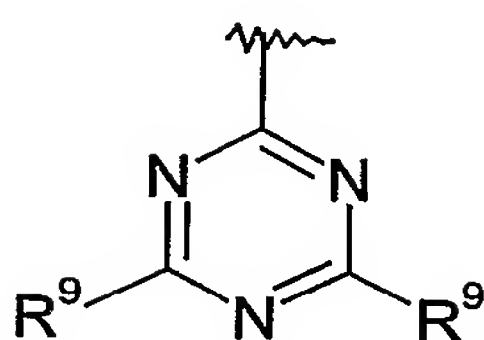
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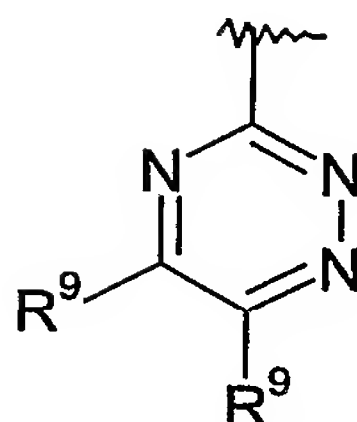
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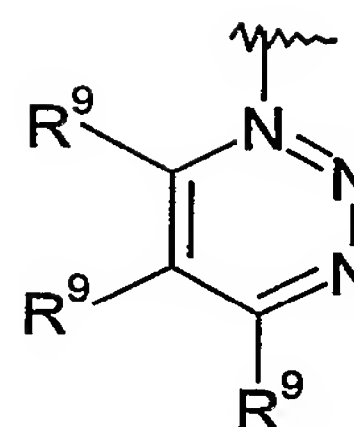
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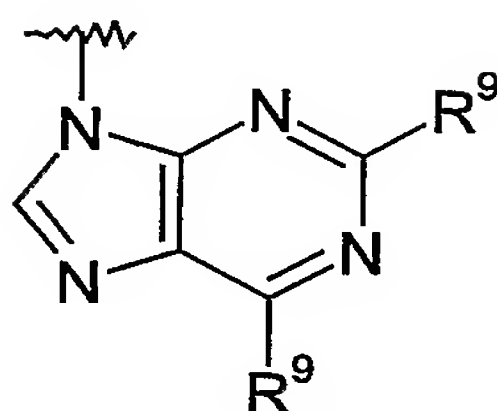
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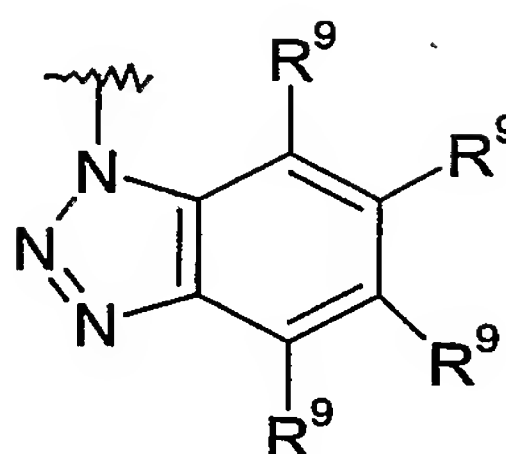
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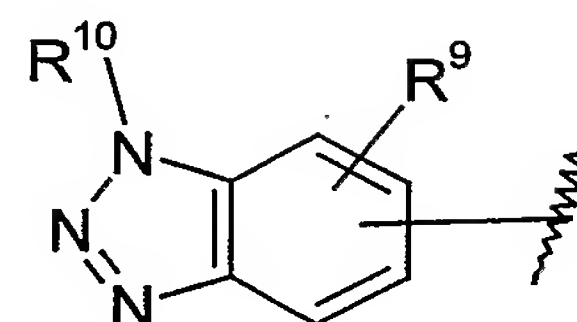
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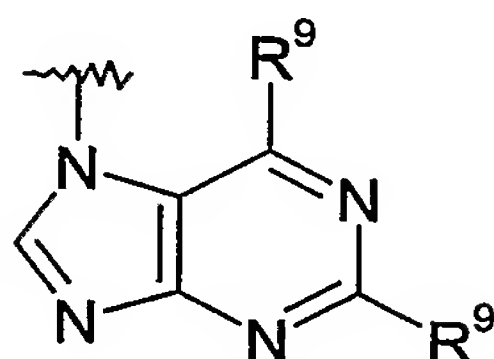
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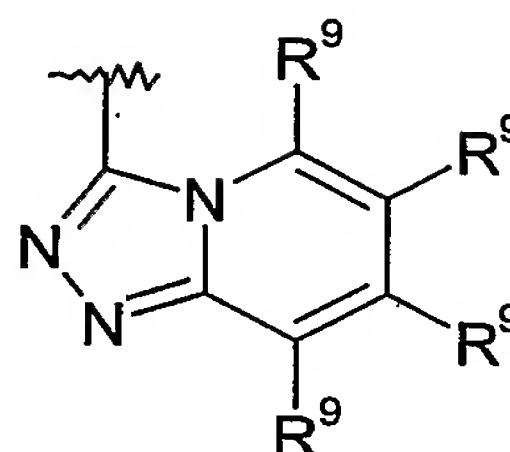
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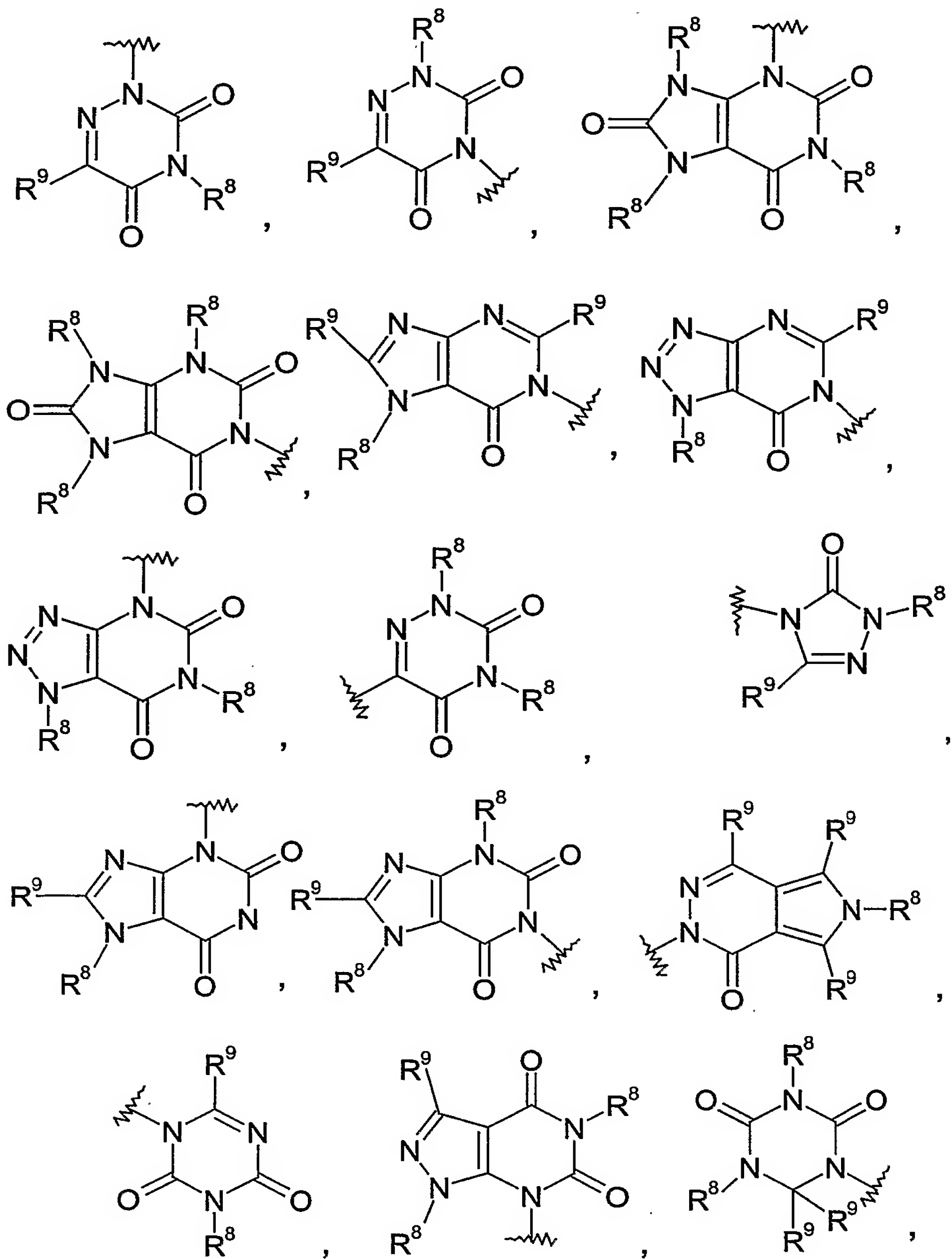
;

wherein  $R^8$  is selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $HO-(C_2-C_6)$ alkyl and  $(C_3-C_8)$ cycloalkyl group;

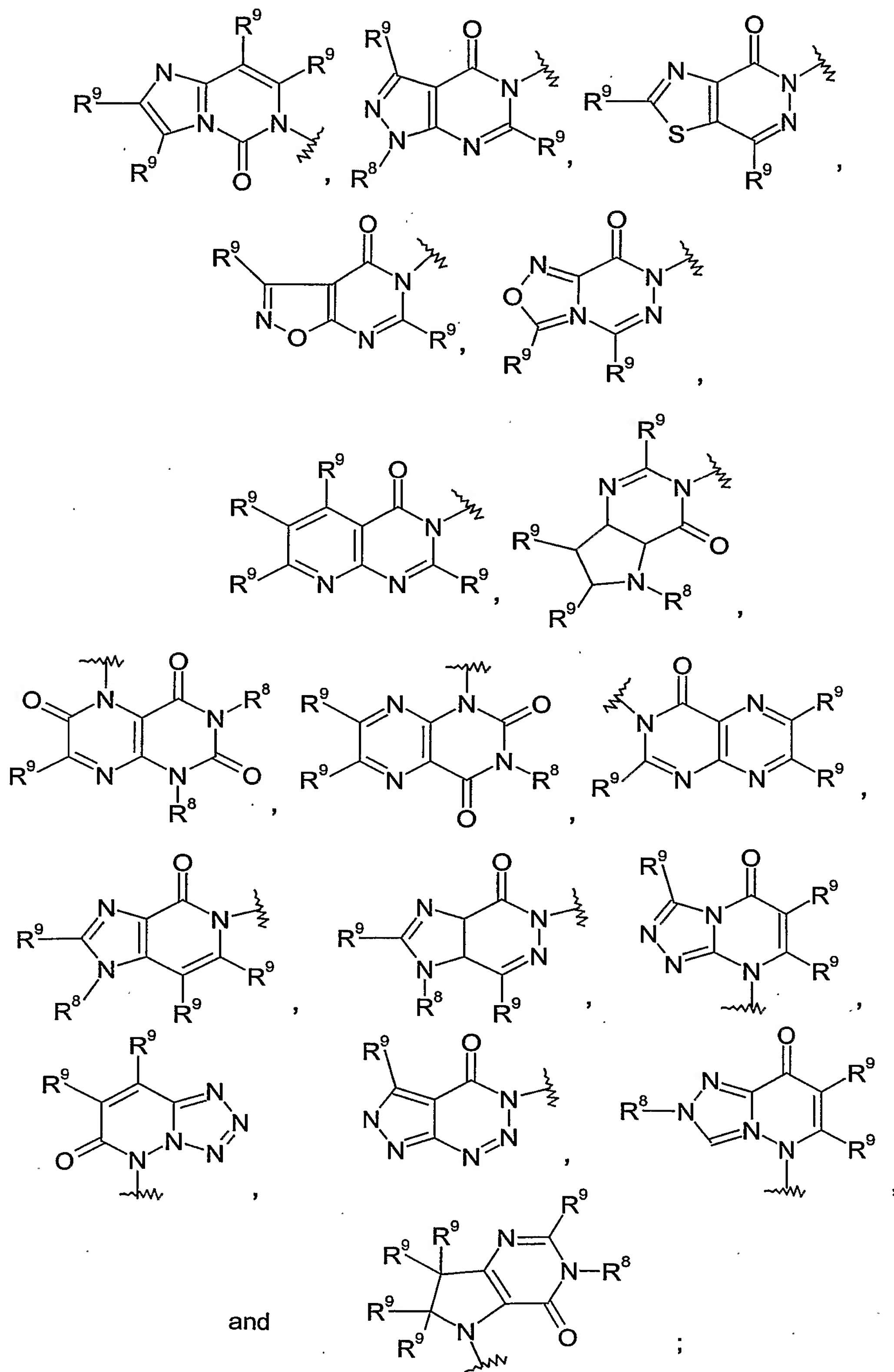
5 wherein  $R^9$  is selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $HO-(C_2-C_6)$ hydroxyalkyl and  $(C_3-C_8)$ cycloalkyl group.

Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide,

pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R<sup>1</sup> is selected from the group



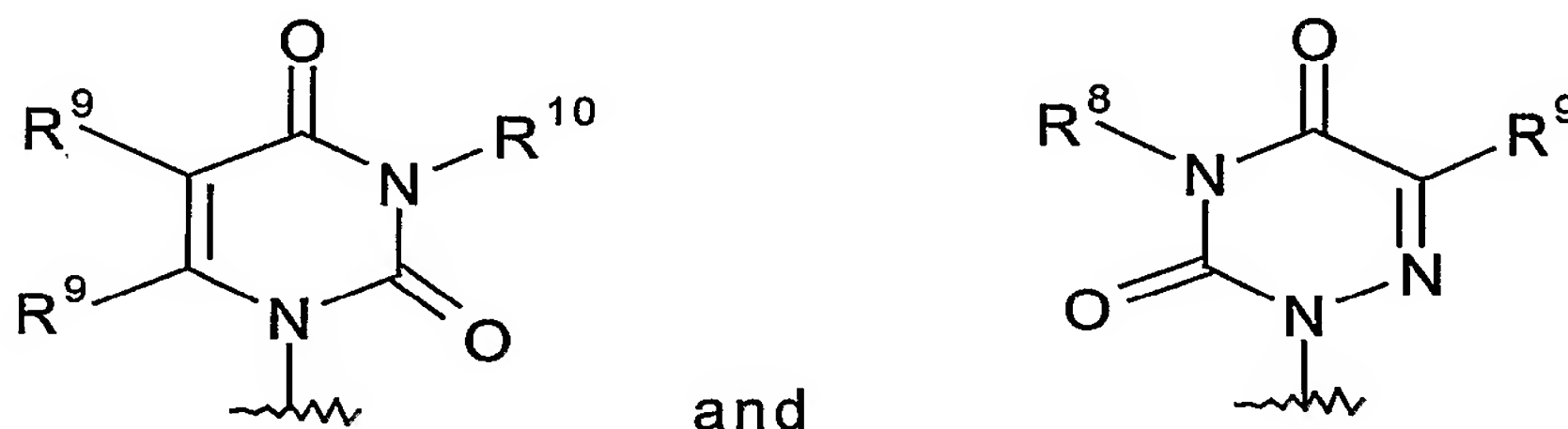




wherein  $R^8$  is selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $HO-(C_2-C_6)$ alkyl and  $(C_3-C_8)$ cycloalkyl group;

wherein  $R^9$  is selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $HO-(C_2-C_6)$ hydroxyalkyl and  $(C_3-C_8)$ cycloalkyl group.

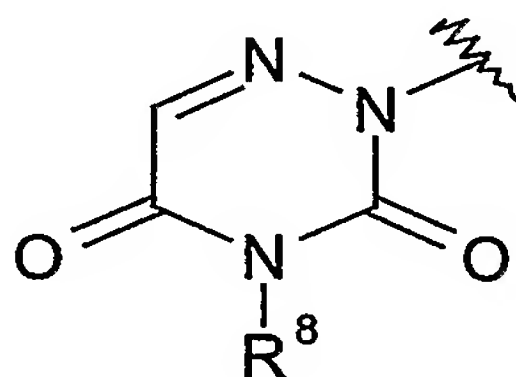
- 5 Another embodiment of the present invention are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is selected from the group



wherein  $R^8$  is selected from the group consisting of hydrogen,  $CF_3$ -,  $(C_1-C_6)$ alkyl,  $HO-(C_2-C_6)$ alkyl or  $(C_3-C_8)$ cycloalkyl group.

wherein  $R^9$  is selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $CF_3-CH_2$ -,  $HO-(C_2-C_6)$ alkyl or  $(C_3-C_8)$ cycloalkyl group.

- 15 Another preferred embodiment of the present invention, referred to as the 6-azauracil compounds, are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein  $R^1$  is



I

20 wherein  $R^8$  is selected from the group consisting of hydrogen or  $(C_1-C_6)$ alkyl.

Another preferred embodiment of the present invention are those compounds of formula I wherein W is a bond.

- 25 Another embodiment of the present invention are those compounds of formula I wherein W is  $-O-$ ,  $-(CH_2)_oO-$ ,  $-O(CH_2)_pO-$ ,  $-(CH_2)_rO(CH_2)_qO-$ ,  $>NR^7$ ,  $-(CH_2)_oNR^7-$ ,  $-O(CH_2)_pNR^7-$ ,  $-(CH_2)_rNR^7(CH_2)_qO-$ ,  $-NR^7(CH_2)_pO-$ ,  $-CONR^7-$ ,  $S(O)_n-$ ,  $-CH_2S(O)_n-$ ,  $-SO_2NR^7-$ , or  $-NR^7SO_2-$ ;

n is 0, 1 or 2;

o is an integer from 1 to 6;

p is an integer from 2 to 6;

q is an integer from 2 to 3;

5 r is an integer from 1 to 3;

$R^7$  represents hydrogen or  $(C_1-C_6)$ alkyl, preferably methyl;

Another embodiment of the present invention are those compounds wherein W is  
 10  $>(C=O)$ ,  $-(CH_2)_o-$ ,  $-CH=$ ,  $-O(CH_2)_o-$ ,  $O(CH_2)_qO(CH_2)_r-$ ,  $-CR^6(OH)-$ ,  $-(CH_2)_rO(CH_2)_r-$ ,  
 $-O(CH_2)_qNR^7(CH_2)_r-$ ,  $-NR^7(CH_2)_o-$ ,  $-(CH_2)_rNR^7(CH_2)_r-$ ,  $-NR^7(CH_2)_qO(CH_2)_r-$ ,  $-NR^7CO-$ , or  
 $-S(O)_nCH_2-$ ;

n is 0, 1 or 2;

o is an integer from 1 to 6;

p is an integer from 2 to 6;

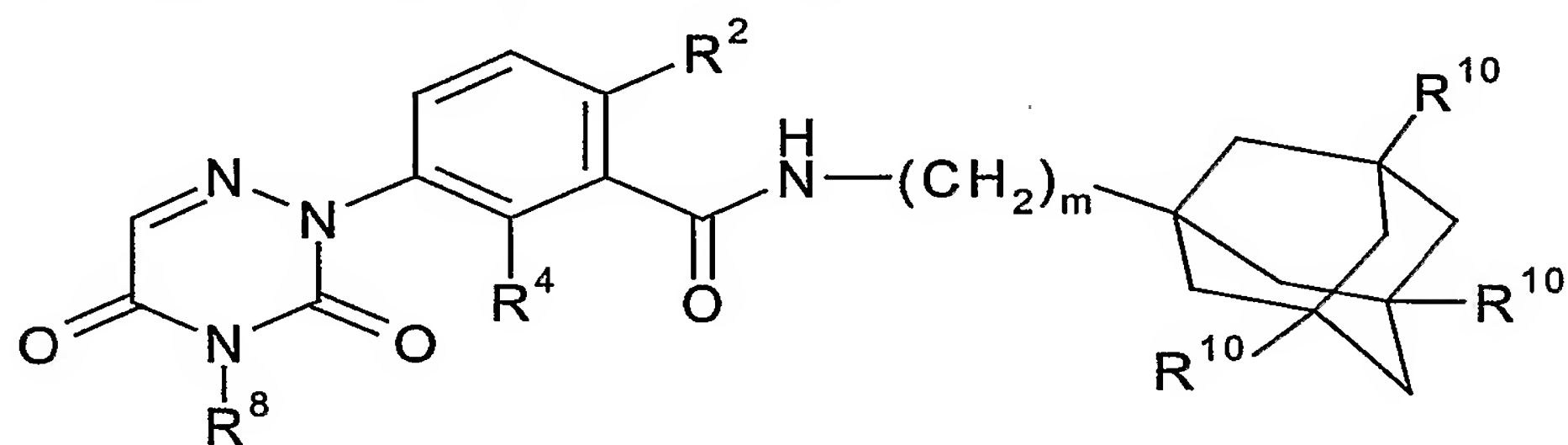
q is an integer from 2 to 3;

15 r is an integer from 1 to 3;

$R^6$  is hydrogen,  $(C_1-C_6)$ alkyl or  $(C_3-C_8)$ cycloalkyl; and

$R^7$  represents hydrogen or  $(C_1-C_6)$ alkyl, preferably methyl.

Another preferred embodiment of the present invention are those compounds of  
 formula I wherein said compound of formula I has the formula



Ia

20

wherein m is an integer from 1 to 2;

$R^2$  is fluoro or chloro;

$R^4$  is selected from the group consisting of hydrogen, halogen, cyano, hydroxyl,  
 $(C_1-C_3)$ alkyl,  $(C_3-C_6)$ cycloalkyl,  $(C_1-C_3)$ alkyloxy,  $-CF_3$ ,  $-OCF_3$  and  $(C_3-C_6)$ cycloalkyloxy;

25  $R^8$  is a hydrogen atom or a  $(C_1-C_6)$ alkyl,  $CF_3-CH_2-$ ,  $HO-(C_2-C_6)$ alkyl or  
 $(C_3-C_8)$ cycloalkyl group;

$R^{10}$  is hydrogen or fluoro;

or a pharmaceutically acceptable salt or solvate thereof.

Examples of specific preferred compounds of the formula I are the following:

- N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide;
- N-Adamantan-1-ylmethyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-methylbenzamide;
- 5 2-Chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-N-tricyclo[4.3.1.1<sup>3,8</sup>]undec-1-ylmethyl-benzamide;
- N-Adamantan-1-ylmethyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-fluorobenzamide;
- N-Adamantan-1-ylmethyl-2-chloro-5-(4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide;
- 10 2-Chloro-N-(3,5-difluoro-adamantan-1-ylmethyl)-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide; and
- N-(2-Adamantan-1-yl-ethyl)-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide.
- 15 Examples of other compounds of the formula I are the following:
- 2-Adamantan-1-yl-N-[2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-phenyl]-acetamide;
- 2-Adamantan-1-yl-N-[5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-methylphenyl]-acetamide;
- 20 N-[2-Chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-phenyl]-2-tricyclo[4.3.1.1<sup>3,8</sup>]undec-1-yl-acetamide;
- 2-Adamantan-1-yl-N-[5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-fluoro-phenyl]-acetamide;
- 2-Adamantan-1-yl-N-[2-chloro-5-(4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-phenyl]-acetamide;
- 25 N-[2-Chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-phenyl]-2-(3,5-difluoro-adamantan-1-yl)-acetamide;
- N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-nicotinamide;
- 30 6-(3,5-Dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-3-methyl-pyridine-2-carboxylic acid (adamantan-1-ylmethyl)-amide;
- N-Adamantan-1-ylmethyl-2-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-5-fluoro-isonicotinamide;
- 5-Chloro-2-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-pyrimidine-4-carboxylic acid
- 35 (tricyclo[4.3.1.1<sup>3,8</sup>]undec-1-ylmethyl)-amide;
- N-Adamantan-1-ylmethyl-2-chloro-5-(5-oxo-4,5-dihydro-[1,2,4]triazol-1-yl)-benzamide;



N-Adamantan-1-ylmethyl-2-chloro-5-(5-oxo-1,5-dihydro-[1,2,4]triazol-4-yl)-benzamide;

N-Adamantan-1-ylmethyl-2-chloro-5-(3-methyl-5-oxo-1,5-dihydro-[1,2,4]triazol-4-yl)-benzamide;

5 N-Adamantan-1-ylmethyl-2-chloro-5-[3-methyl-5-oxo-1-(2,2,2-trifluoro-ethyl)-1,5-dihydro-[1,2,4]triazol-4-yl]-benzamide;

N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-benzamide;

10 N-Adamantan-1-ylmethyl-2-chloro-5-(2-methyl-3,5-dioxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-benzamide;

N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazin-6-yl)-benzamide; and

N-Adamantan-1-ylmethyl-5-(2,4-dioxo-3,4-dihydro-2H-[1,3,5]triazin-1-yl)-2-fluoro-benzamide.

15 The present invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen,  
20 phosphorous, fluorine and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example  
25 those into which radioactive isotopes such as  $^3\text{H}$  and  $^{14}\text{C}$  are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e.,  $^3\text{H}$ , and carbon-14, i.e.,  $^{14}\text{C}$ , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e.,  $^2\text{H}$ , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or  
30 reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labelled reagent for a non-isotopically-labelled reagent.

35 The compounds of Formula I or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or

unregulated cytokine production by such mammal's cells, such as but not limited to monocytes and/or macrophages.

The present invention relates to a method for treating a P2X<sub>7</sub> mediated disease in a mammal in need thereof, which comprises administering to said mammal an effective amount  
5 of a compound of formula I.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis (including psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and acute synovitis), inflammatory bowel disease, Crohn's disease, emphysema, acute  
10 respiratory distress syndrome, adult respiratory distress syndrome, asthma, bronchitis chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, allergic reactions, allergic contact hypersensitivity, eczema, contact dermatitis, psoriasis, sunburn, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, bone resorption disease, loosening of artificial joint implants,  
15 atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, neurotrauma, spinal cord injury, neuro-degenerative disorders, Alzheimer's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, corneal scarring,  
20 scleritis, abnormal wound healing, burns, autoimmune disorders, Huntington's disease, diabetes, AIDS, cachexia, sepsis, septic shock, endotoxic shock, conjunctivitis shock, gram negative sepsis, toxic shock syndrome, cerebral malaria, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, graft vs. host reaction, allograft rejection, organ transplant toxicity, ulcerative colitis, or muscle degeneration, in a mammal, including a human, comprising  
25 administering to said mammal an amount of a compound to formula I, effective in treating such a condition.

The present invention relates to a pharmaceutical composition for the treatment of a P2X<sub>7</sub> mediated disease in a mammal which comprises an effective amount of a compound according to formula I and a pharmaceutically acceptable carrier.

30 The present invention relates to a pharmaceutical composition for the treatment of a condition selected from the group consisting of arthritis (including psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and acute synovitis), inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, adult respiratory distress  
35 syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, allergic reactions, allergic contact hypersensitivity, eczema, contact dermatitis, psoriasis, sunburn, cancer, tissue ulceration,

restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, bone resorption disease, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, neurotrauma, spinal cord injury, neuro-degenerative disorders, Alzheimer's disease, Parkinson's disease, migraine, depression, 5 peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, corneal scarring, scleritis, abnormal wound healing, burns, autoimmune disorders, Huntington's disease, diabetes, AIDS, cachexia, sepsis, septic shock, endotoxic shock, conjunctivitis shock, gram negative sepsis, toxic shock syndrome, cerebral malaria, 10 cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, graft vs. host reaction, allograft rejection, organ transplant toxicity, ulcerative colitis, or muscle degeneration in a mammal, including a human, comprising an amount of a compound to formula I, effective in treating such a condition and a pharmaceutically acceptable carrier.

Preferably, the compounds of the invention are useful for the treatment of rheumatoid 15 arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, chronic obstructive pulmonary disease (COPD), hyperresponsiveness of the airway, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukemia, diabetes, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischemic heart disease, stroke and varicose veins.

20 The present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

25 The invention further provides a method of treating osteoarthritis which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis or psoriasis) which 30 comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, 35 as hereinbefore defined to a patient.

The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more

symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as  
5 hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a  
10 pharmaceutically acceptable adjuvant, diluent or carrier.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 1 mg to 1 gram, preferably 1 mg to 250 mg, more  
15 preferably 10 mg to 100 mg.

The present invention also encompasses sustained release compositions.

The present invention also relates to processes of preparing the compounds of formula I and intermediates used in such processes.

One of ordinary skill in the art will appreciate that the compounds of the invention are  
20 useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the compounds of the invention may be  
25 combined with agents such as TNF- $\alpha$  inhibitors such as anti-TNF monoclonal antibodies (such as Remicade, CDP-870 and D<sub>2</sub>E<sub>7</sub>) and TNF receptor immunoglobulin molecules (such as Enbrel®), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib) low dose methotrexate, lefunomide; ciclesonide; hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The present invention still further relates to the combination of a compound of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist selected from the group consisting of zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-*tert*-butylphenol hydrazones;  
35 methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2-cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline



compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

5 The present invention still further relates to the combination of a compound of the invention together with a receptor antagonists for leukotrienes LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> selected from the group consisting of the phenothiazin-3-ones such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

10 The present invention still further relates to the combination of a compound of the invention together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

The present invention still further relates to the combination of a compound of the invention together with a antihistaminic H<sub>1</sub> receptor antagonists including cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

15 The present invention still further relates to the combination of a compound of the invention together with a gastroprotective H<sub>2</sub> receptor antagonist.

The present invention still further relates to the combination of a compound of the invention together with an  $\alpha_1$ - and  $\alpha_2$ -adrenoceptor agonist vasoconstrictor sympathomimetic agent, including propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

20

The present invention still further relates to the combination of a compound of the invention together with anticholinergic agents including ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine.

25 The present invention still further relates to the combination of a compound of the invention together with a  $\beta_1$ - to  $\beta_4$ -adrenoceptor agonists including metaproterenol, isoproterenol; isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol; or methylxanthanines including theophylline and aminophylline; sodium cromoglycate; or muscarinic receptor (M1, M2, and M3) antagonist.

30

The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the invention together with an inhaled glucocorticoid with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate.

35



The present invention still further relates to the combination of a compound of the invention together with (a) tryptase inhibitors; (b) platelet activating factor (PAF) antagonists; (c) interleukin converting enzyme (ICE) inhibitors; (d) IMPDH inhibitors; (e) adhesion molecule inhibitors including VLA-4 antagonists; (f) cathepsins; (g) MAP kinase inhibitors; (h) glucose-6  
5 phosphate dehydrogenase inhibitors; (i) kinin-B<sub>1</sub> - and B<sub>2</sub> -receptor antagonists; (j) anti-gout agents, *e.g.*, colchicine; (k) xanthine oxidase inhibitors, *e.g.*, allopurinol; (l) uricosuric agents, *e.g.*, probenecid, sulfinpyrazone, and benzbromarone; (m) growth hormone secretagogues; (n) transforming growth factor (TGF $\beta$ ); (o) platelet-derived growth factor (PDGF); (p) fibroblast growth factor, *e.g.*, basic fibroblast growth factor (bFGF); (q) granulocyte macrophage colony  
10 stimulating factor (GM-CSF); (r) capsaicin cream; (s) Tachykinin NK<sub>1</sub> and NK<sub>3</sub> receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; and (t) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892.

The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), *i.e.*, the stromelysins,  
15 the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11).

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in  
20 combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular  
25 therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and farnesyl transferase inhibitors, VegF  
inhibitors, COX-2 inhibitors and antimetabolites such as methotrexate antineoplastic agents,  
30 especially antimitotic drugs including the vinca alkaloids such as vinblastine and vincristine;

The compounds of the invention may also be used in combination with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antisepsis compounds such as Valant.

The compounds of the present invention may also be used in combination with  
35 cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

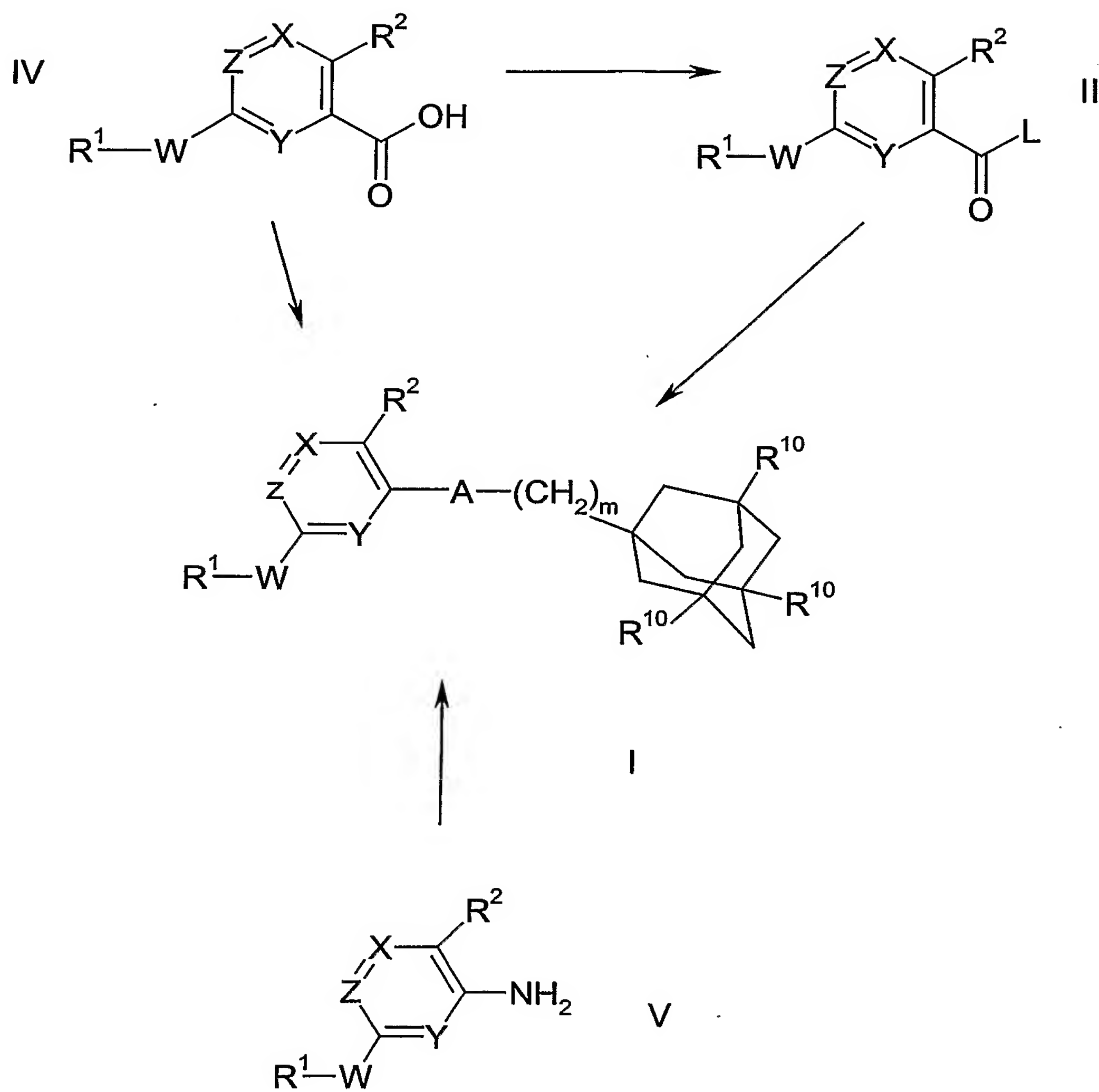
The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, 5 Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and 10 immunosuppressant agents such as FK-506, rapamycin, cyclosporine, azathioprine, and methotrexate;.

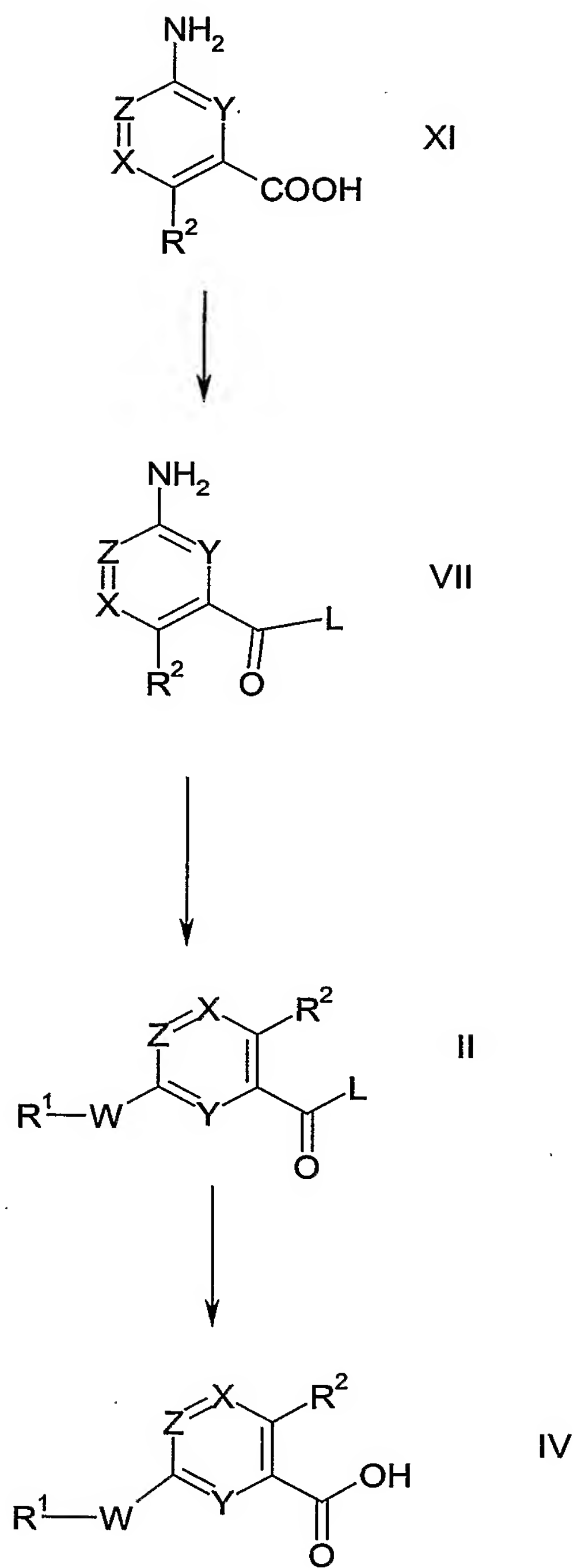
#### Detailed Description of the Invention

Compounds of the formula I may be prepared according to the following reaction schemes and discussion. Unless otherwise indicated A, X, Y, Z, W, m, n, o, p, q, r, and R<sup>1</sup> 15 through R<sup>10</sup> and structural formula I in the reaction schemes and discussion that follow are as defined above.

Scheme 1

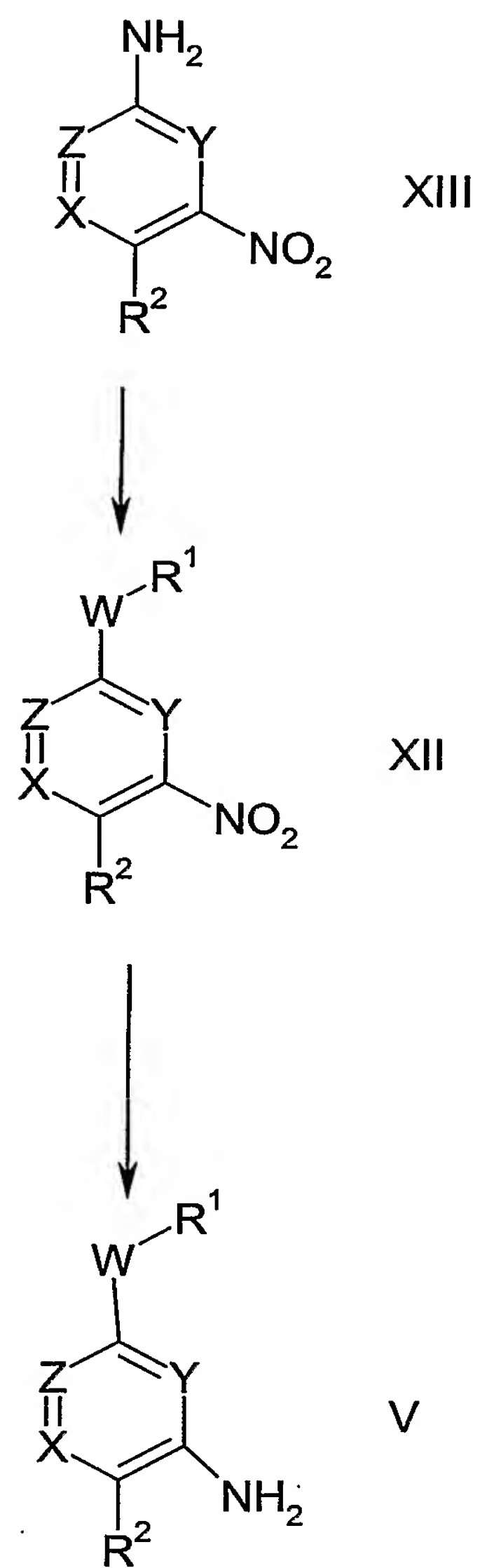


Scheme 2

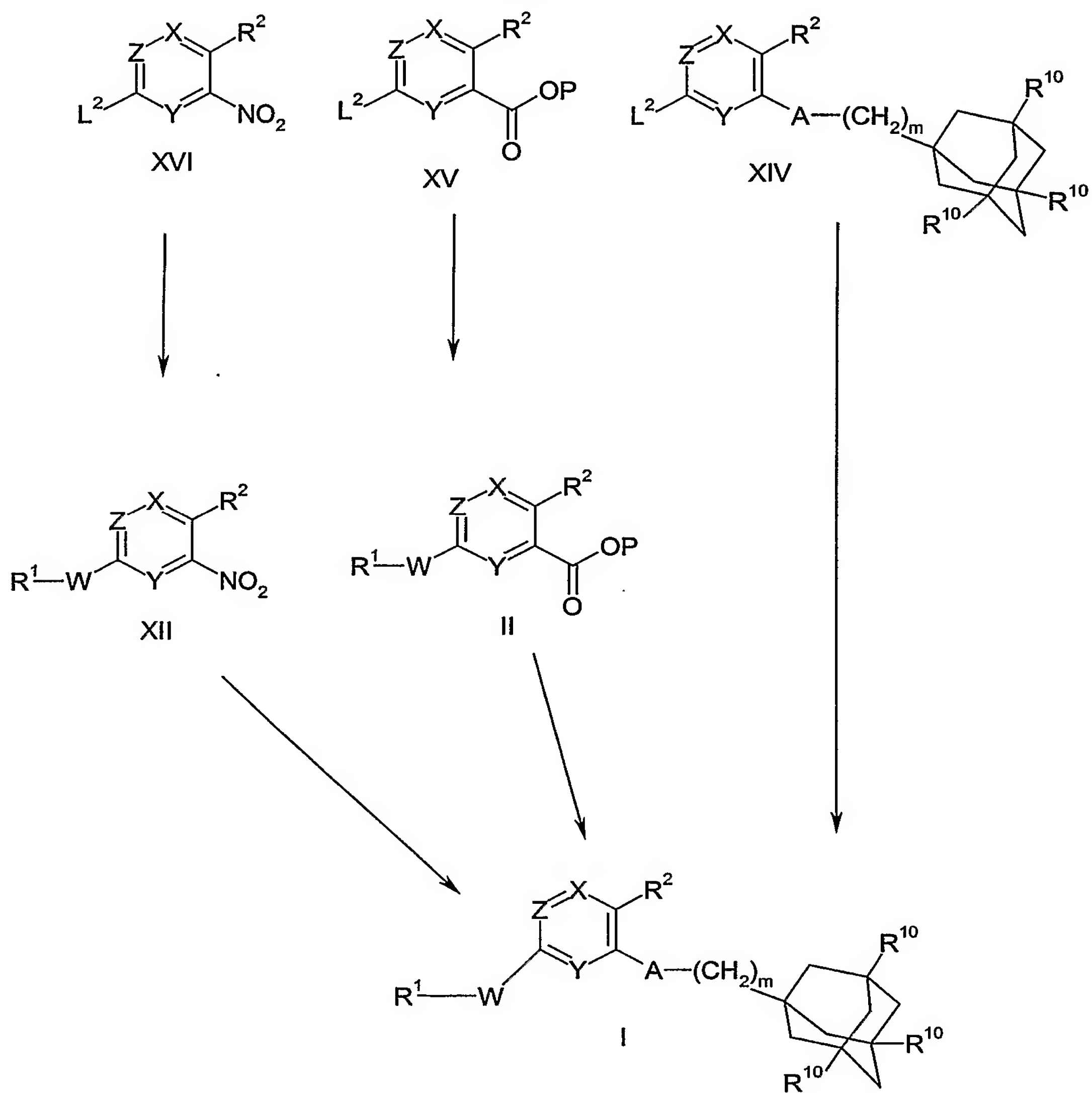




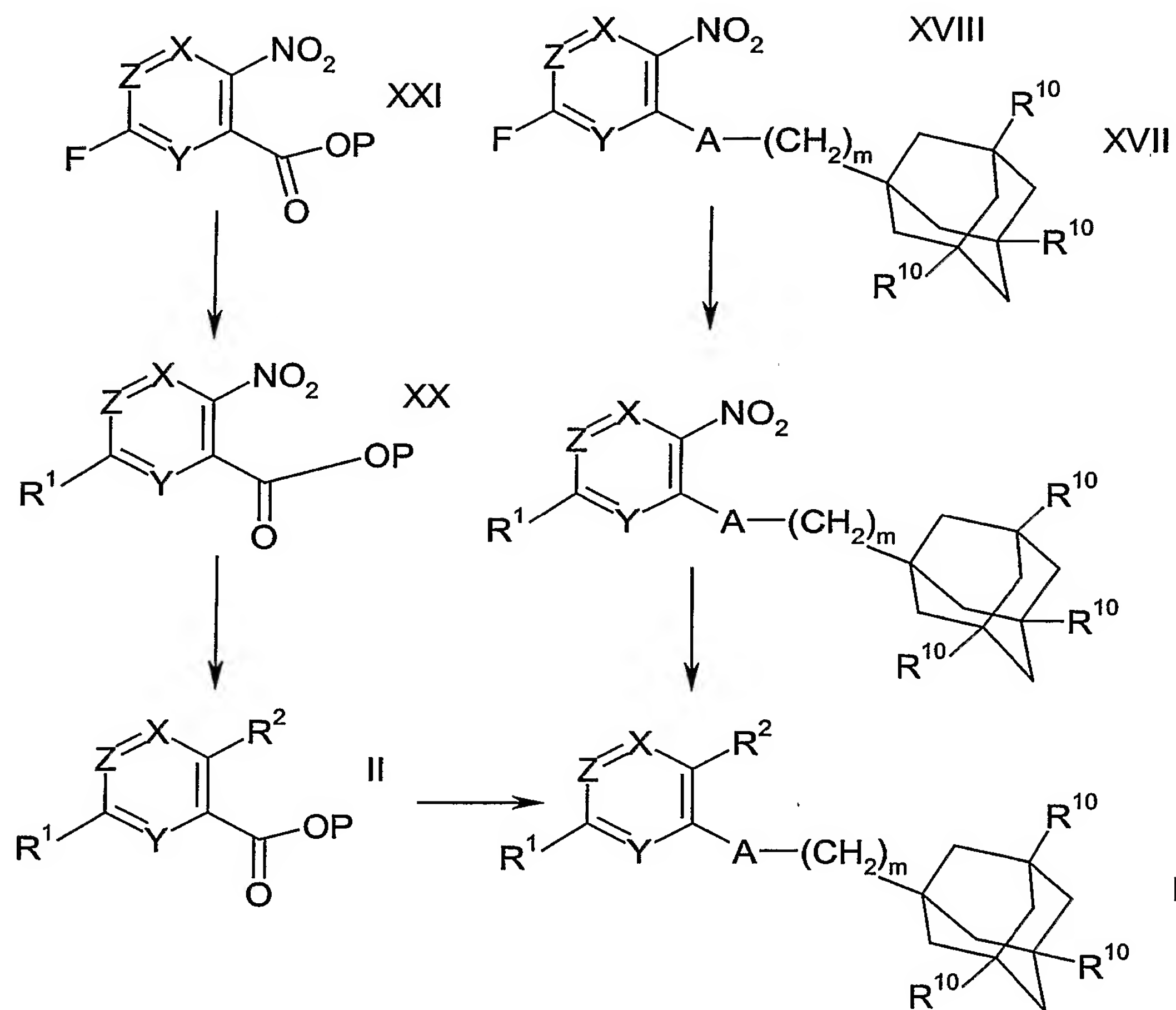
Scheme 3



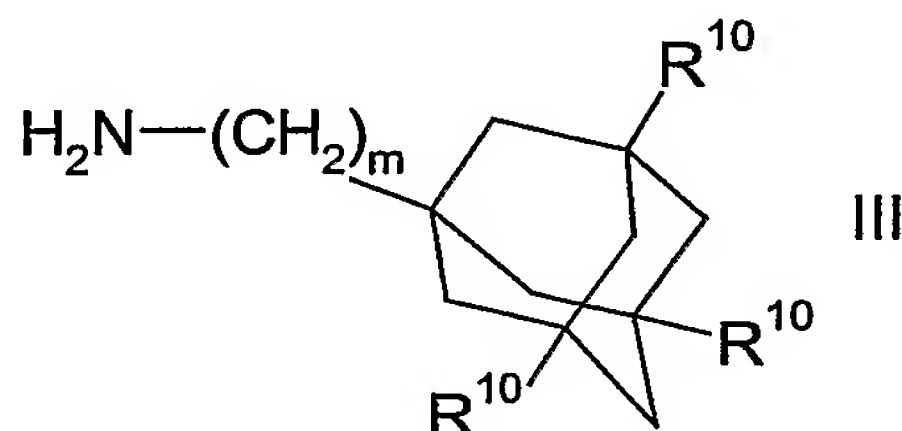
Scheme 4



Scheme 5



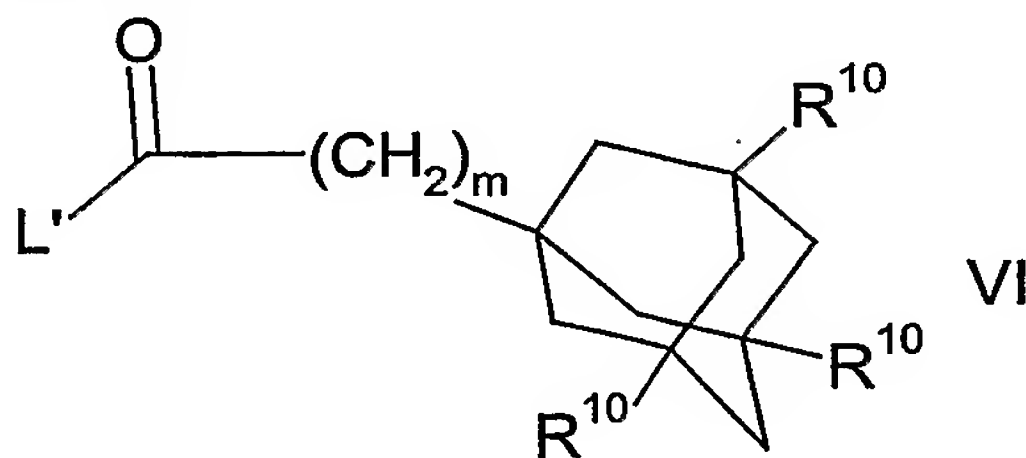
Scheme 1 refers to the preparation of compounds of formula I. Compounds of formula I, wherein A is  $-(C=O)-NH-$ , can be prepared from compounds of formula II, wherein L is a halo or an anhydride leaving group of the formula  $R-(C=O)-O-$  wherein R is optionally substituted alkyl or aryl, by reaction with a compound of formula III



in the presence of a base. Suitable bases include an excess of compound of formula III as well as triethylamine, dimethylaminopyridine, sodium carbonate, pyridine, and Hünigs base, preferably triethylamine. The aforesaid reaction may be performed neat or in the presence of a solvent. Suitable solvents include methylene chloride, tetrahydrofuran, and toluene, preferably methylene chloride.

Alternatively, compounds of formula I, wherein A is  $-C=ONH-$ , can be prepared from compounds of formula IV, by reaction with a compound of formula III in the presence of a coupling reagent, such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) or dicyclohexyl carbodiimide (DCC) and hydroxybenzotriazole hydrate (HOBt), and a base, such as diisopropylethylamine (DIEA) or triethylamine, in an aprotic solvent, such as methylene chloride. Suitable solvents include methylene chloride and dimethyl formamide, preferably methylene chloride. The aforesaid reaction may be run at a temperature from about 0°C to about 50°C, for a period from about 1 hour to about 16 hours (as illustrated in Comprehensive Organic Transformation, R.C. Larock, VCH Publisher, Inc. (1989) pp. 972-976).

Compounds of formula I, wherein A is  $-NH-(C=O)-$ , may be prepared from compounds of formula V by reaction with a compound of the formula VI



wherein L' is a leaving group such as chloro, fluoro, bromo, or an anhydride leaving group of the formula  $R-(C=O)-O-$ , wherein R is optionally substituted alkyl or aryl. The aforesaid reaction may be conducted in the presence of a suitable base. Suitable bases include an excess of compound of formula V as well as triethylamine, dimethylaminopyridine, sodium carbonate, pyridine, and Hünigs base, preferably triethylamine. The aforesaid reaction may be performed neat or in the presence of a solvent at a temperature from about 0°C to about



50°C, for a period from about 10 minutes to about 16 hours. Suitable solvents include methylene chloride, tetrahydrofuran, and toluene, preferably methylene chloride.

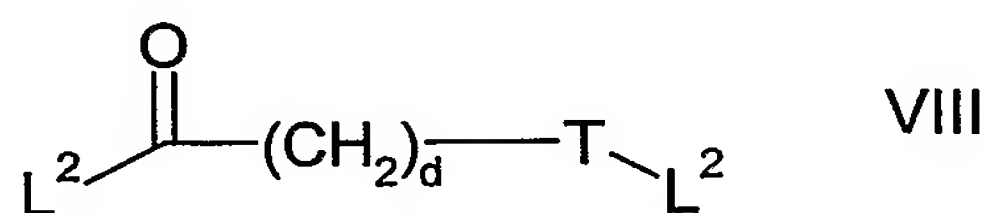
Compounds of formula II and IV can be made according to the methods of Scheme 2.

Compounds of formula V can be made according to the methods of Scheme 3.

5 Scheme 2 refers to the preparation of compounds of formulae IV and II, wherein L is a leaving group, W is a bond,  $>NR^7$ ,  $-(CH_2)_oNR^7-$ ,  $-O(CH_2)_pNR^7-$ ,  $-CONR^7-$  or  $-SO_2NR^7-$ ; and  $R^1$  is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring. Compounds of formulae II and IV can be converted into compounds of formula I according to the methods of Scheme 1.

10 Referring to Scheme 2, a compound of the formula IV, wherein W is a bond,  $>NR^7$ ,  $-(CH_2)_oNR^7-$ ,  $-O(CH_2)_pNR^7-$ ,  $-CONR^7-$  or  $-SO_2NR^7-$ ; can be prepared from a compound of the formula II, wherein L is a leaving group such as a methoxy or ethoxy, by reaction with a saponification reagent such as with an aqueous base, such as sodium hydroxide in an alcoholic solvent such as methanol, ethanol or tert.-butanol. The aforesaid reaction may be  
15 run at a temperature from about 0°C to about 100°C, for a period from about 1 hour to about 24 hours. When L is a leaving group such as tert.-butyl ester, a compound of the formula IV can be prepared by the reaction of a compound of a compound of formula II with an acid such as hydrochloric acid in a solvent such as dioxane at a temperature between 25°C to about 80°C, for a period from about 10 minutes to about 6 hours.

20 A compound of the formula II, wherein L is a leaving group such as alkoxy, W is a bond and  $R^1$  is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, can be prepared from a compound of the formula VII by reaction with a compound of the formula

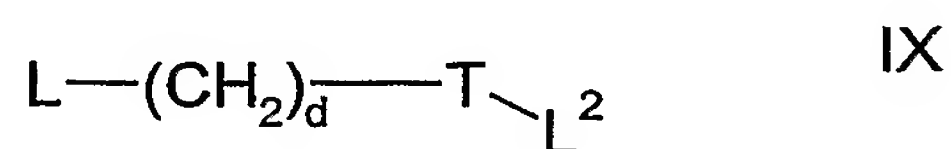


25 wherein d is 2 to 8 and wherein any of said  $-CH_2-$  groups may be optionally substituted by one or two  $R^9$  substituents, and wherein at least two of said  $-CH_2-$  groups are replaced with  $-NR^{10}-$  (up to five  $-NR^{10}-$ ) and may optionally additionally contain 0-3 heteroatoms independently selected from the group consisting of  $-O-$  and  $-S(O)_n-$ , wherein n is an integer from zero to 2; or any single bond between any two  $CH_2$  groups may optionally be a double  
30 bond; T is  $>C=O$  or  $>SO_2$ ; wherein any carbon atom of said  $-(CH_2)_d-$  may optionally contain an oxo group and each  $L^2$  is independently hydrogen,  $(C_1-C_6)$ alkyl or halo; under reductive amination conditions. The reductive amination is typically carried out with a reducing agent, such as sodium cyanoborohydride or sodium triacetoxyborohydride, preferably at a pH of between 6 and 8. The reaction is normally performed in a protic solvent, such as methanol or  
35 ethanol, or in a mixture of solvents, such as dichloroethane/methanol, at temperature of about

-78°C to about 40°C for a period from about 1 hour to about 24 hours. (See A. Abdel-Magid, C. Maryanoff, K. Carson, Tetrahedron Lett., Vol. 34, Issue 31, 5595-98, 1990). Other conditions involve the use of titanium isopropoxide and sodium cyanoborohydride (R.J.Mattson et al., J.Org.Chem., 1990, 55, 2552-4) or involve the formation of the imine under dehydrating conditions followed by reduction (Comprehensive Organic Transformation, R.C. Larock, VCH Publisher, Inc (1989) pp. 421-425).

Alternatively, a compound of the formula II, wherein L is a leaving group such as alkoxy, and R<sup>1</sup> is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, can be prepared from the diazonium intermediate derived from a compound of the formula VII. The diazonium intermediate is prepared by reaction of a compound of the formula VII with an acid such as hydrochloric acid followed by treatment with sodium nitrite in a solvent such as glacial acetic acid at a temperature from about 0°C to about 30°C, and the reaction is generally run for a period of about 30 min to about 3 hours. The compound of the formula II is prepared by the reaction of the above diazonium intermediate with a compound of the formula VIII wherein d is 2 to 8 and wherein any of said -CH<sub>2</sub>- groups may be optionally substituted by one or two R<sup>9</sup> substituents, and wherein at least two of said -CH<sub>2</sub>- groups are replaced with -NR<sup>10</sup>- (up to five -NR<sup>10</sup>-) and may optionally additionally contain 0-3 heteroatoms independently selected from the group consisting of -O- and -S(O)<sub>n</sub>-, wherein n is an integer from zero to 2; or any single bond between any two CH<sub>2</sub> groups may optionally be a double bond; T is >C=O or >SO<sub>2</sub>; wherein any carbon atom of said -(CH<sub>2</sub>)<sub>d</sub>- may optionally contain an oxo group, and wherein any of said -CH<sub>2</sub>- groups may optionally be replaced with either an oxo group or a heteroatom selected from -O- or -S(O)<sub>n</sub>-, wherein n is an integer from zero to 2; or any single bond between any two CH<sub>2</sub> groups may optionally be a double bond; T is >C=O or >SO<sub>2</sub>; and each L<sup>2</sup> is independently alkoxy or halo; under basic conditions. The reaction is typically carried out with sodium acetate as base at a temperature from about 0°C to about 120°C, and the reaction is generally run for a period of about 1 hour to about 24 hours. (For example, see R. D. Carroll et al., J. Med. Chem., 1983, 26, 96-100).

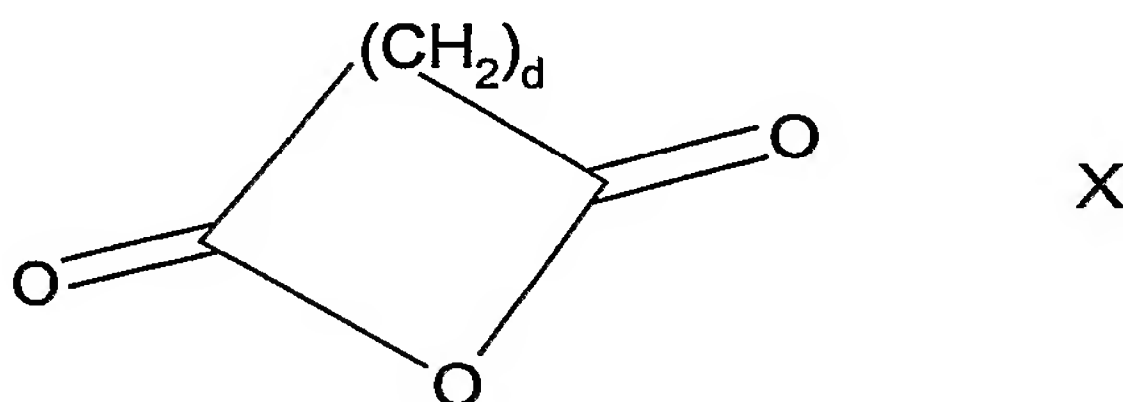
Alternatively, one skilled in the art will also appreciate that a compound of formula II wherein W is a bond and R<sup>1</sup> is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, can be prepared by standard synthetic methods from a compound of the formula VII, wherein L is a protecting group such as alkoxy, by reaction with a bidentate reagent wherein two different transformable groups exist, such as an alkylating and acylating group of the formula



wherein L is a leaving group such as halo, L<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl or halo; wherein d is 2 to 8 and wherein any of said -CH<sub>2</sub>- groups may be optionally substituted by one or two R<sup>9</sup>

substituents, and wherein at least two of said  $-\text{CH}_2-$  groups are replaced with  $-\text{NR}^{10}-$  (up to five  $-\text{NR}^{10}-$ ) and may optionally additionally contain 0-3 heteroatoms independently selected from the group consisting of  $-\text{O}-$  and  $-\text{S}(\text{O})_n-$ , wherein  $n$  is an integer from zero to 2; or any single bond between any two  $\text{CH}_2$  groups may optionally be a double bond;  $\text{T}$  is  $>\text{C}=\text{O}$  or  $>\text{SO}_2$ ; wherein any carbon atom of said  $-(\text{CH}_2)_d-$  may optionally contain an oxo group; or any single bond between any two  $\text{CH}_2$  groups may optionally be a double bond.

Alternatively, one skilled in the art will also appreciate that a compound of formula II wherein  $\text{R}^1$  is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, wherein the bridgehead atom is nitrogen, can be prepared by standard synthetic methods from a compound of the formula VII, wherein  $\text{L}$  is a protecting group such as alkoxy, by reaction with an anhydride reagent of the formula



wherein  $d$  is 2 to 8 and wherein any of said  $-\text{CH}_2-$  groups may be optionally substituted by one or two  $\text{R}^9$  substituents, and wherein at least two of said  $-\text{CH}_2-$  groups are replaced with  $-\text{NR}^{10}-$  (up to five  $-\text{NR}^{10}-$ ) and may optionally additionally contain 0-3 heteroatoms independently selected from the group consisting of  $-\text{O}-$  and  $-\text{S}(\text{O})_n-$ , wherein  $n$  is an integer from zero to 2; or any single bond between any two  $\text{CH}_2$  groups may optionally be a double bond; wherein any carbon atom of said  $-(\text{CH}_2)_d-$  may optionally contain an oxo group; or any single bond between any two  $\text{CH}_2$  groups may optionally be a double bond.

Alternatively, one skilled in the art will also appreciate that a compound of formula II wherein  $\text{W}$  is  $>\text{NR}^7$ ,  $-(\text{CH}_2)_o\text{NR}^7-$ ,  $-\text{O}(\text{CH}_2)_p\text{NR}^7-$ ,  $-\text{SO}_2\text{NR}^7-$  or  $-\text{CONR}^7-$ ; can be prepared by reaction of a compound of formula VII with a compound of the formula  $\text{R}^1-\text{W}'-\text{L}$ , wherein  $\text{W}'-\text{L}$  is halogen, triflate,  $-(\text{CH}_2)_o\text{-halo}$ ,  $-(\text{CH}_2)_o\text{-Tosyl}$ ,  $-\text{O}(\text{CH}_2)_p\text{-halo}$ ,  $-\text{O}(\text{CH}_2)_p\text{-Tosyl}$ ,  $-(\text{CH}_2)_o(\text{C}=\text{O})\text{H}-$ ,  $-\text{O}-(\text{CH}_2)_o(\text{C}=\text{O})\text{H}-$ ,  $-\text{SO}_2\text{-Cl}$ ,  $-\text{CO}_2\text{H}$ ,  $-(\text{C}=\text{O})\text{-Cl}$ , or  $-(\text{C}=\text{O})\text{H}-$ ; wherein  $\text{R}^7$  is hydrogen. Compounds of formula II wherein  $\text{R}^7$  is other than hydrogen can be prepared from compounds of formula II wherein  $\text{R}^7$  is hydrogen by using standard transformations or coupling methods such as alkylation, acylation, reductive amination or sulfonylation. Such methods are well known to those skilled in the art and are described in standard organic chemistry text books such as March, Advanced Organic Chemistry, 641-676 (John Wiley & Sons, Inc., Fourth Edition, 1992).

Compounds of the formula VII can be prepared from compounds of the formula XI by reaction with an alcohol of the formula  $\text{ROH}$ , wherein  $\text{R}$  is optionally substituted  $(\text{C}_1\text{-C}_4)\text{alkyl}$  or  $(\text{C}_6\text{-C}_{10})\text{aryl}$ , in the presence of an acid (a so called Fischer esterification) or a coupling

reagent, such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) or dicyclohexyl carbodiimide (DCC) and hydroxybenzotriazole hydrate (HOBt), and a base, such as diisopropylethylamine (DIEA) or triethylamine, in an aprotic solvent, such as methylene chloride. Suitable solvents include methylene chloride and dimethyl formamide, preferably methylene chloride. The aforesaid reaction may be run at a temperature from about 0°C to about 50°C, for a period from about 1 hour to about 16 hours (as illustrated in Comprehensive Organic Transformation, R.C. Larock, VCH Publisher, Inc. (1989) pp. 972-976).

Compounds of the formulae VIII, IX, X and XI are commercially available or can be made by methods well known to those of ordinary skill in the art.

Scheme 3 refers to the preparation of the compounds of formula V which are intermediates useful in the preparation of compound of formula I, in Scheme 1. Referring to Scheme 3, a compound of formula V is prepared by reduction of a compound of the formula XII. Reduction may be effected with hydrogen gas (H<sub>2</sub>), using catalysts such as palladium on carbon (Pd/C), palladium on barium sulfate (Pd/BaSO<sub>4</sub>), platinum on carbon (Pt/C), or tris(triphenylphosphine) rhodium chloride (Wilkinson's catalyst), in an appropriate solvent such as methanol, ethanol, THF, dioxane or ethyl acetate, at a pressure from about 1 to about 5 atmospheres and a temperature from about 10°C to about 60°C, as described in Catalytic Hydrogenation in Organic Synthesis, Paul Rylander, Academic Press Inc., San Diego, 31-63 (1979). The following conditions are preferred: Pd on carbon, methanol at 25°C and 50 psi of hydrogen gas pressure.

An alternative procedure employing the use of reagents such as ammonium formate and Pd/C in methanol at the reflux temperature under an inert atmosphere (e.g., nitrogen or argon gas) is also effective.

Another alternative reduction procedure, for use when R<sup>1</sup> contains a group incompatible with the above hydrogenation conditions (e.g., an olefin or halide group), is a dissolving metal reduction wherein the compound of formula XII is treated with a metal, such as zinc, tin or iron, in the presence of an acid such as hydrochloric or sulfuric acid. The aforesaid reaction may be run at a temperature from about 0°C to about 100°C, for a period from about 1 hour to about 16 hours.

Compounds of the formula XII can be prepared from compounds of formula XIII by reaction with reagents of the formulae VIII, IX and X as described previously in Scheme 2 for the conversion of a compound of formula VII to II.

The starting materials of the formula XIII are either commercially available or known in the art.

Scheme 4 refers to alternate preparations of compounds of formula I.

Referring to Scheme 4, compounds of the formula I, wherein R<sup>1</sup> is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, can be prepared



by an aryl palladium coupling reaction. Aryl palladium coupling reactions are well known to those skilled in the art. One well known coupling method, so called Buchwald and Hartwig conditions, involves the coupling of a compound of formula XIV, wherein  $L^2$  is Cl, Br, I or triflate (TfO), with a compound of the formula  $R^1-H$ , wherein H is a hydrogen on a nitrogen ring atom, in the presence of a palladium (0) catalyst and a base. Palladium (0) catalysts include tris(dibenzylidene acetone)dipalladium(O) ( $Pd_2(dba)_3$ ), di(dibenzylidene acetone) palladium(O) ( $Pd(dba)_2$ ), palladium acetate ( $Pd(OAc)_2$ ), and a suitable ligand, such as a triaryl phosphine ligand, tri(*t*-butyl)phosphine, 1,1'-bis(diphenylphosphanyl)ferrocene (DPPF), 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP), or PHANEPHOS, preferably tri(*ortho*-tolyl)phosphine. Suitable bases include  $K_2CO_3$ ,  $K_2PO_4$ ,  $CsCO_3$ ,  $LiN(TMS)_2$  or an alkoxide base such as sodium methoxide, sodium ethoxide, potassium *t*-butoxide, preferably sodium *tert*-butoxide. Suitable solvents include toluene or an ethereal solvent, preferably dioxane. The aforesaid reaction may be run at a temperature of about 40°C to 110°C for about 1 to 48 hours. Such conditions are reviewed in *Angew. Chem. Int. Ed. Engl.*, 1998, 37, 2046-2067 and are well known to those of ordinary skill in the art. Preferred Buchwald conditions use palladium acetate ( $Pd(OAc)_2$ ) or palladium tetra-triphenylphosphine ( $Pd(PPh_3)_4$ ) as the source of the palladium. Suitable solvents include THF, toluene or ethereal solvents. The aforesaid reaction may be run at a temperature of about 25°C to 110°C for about 1 to 4 hours, preferably 2 hours. Nickel catalysts, such as Ni(cod) (nickel 1,5-cyclooctadiene), are also well known.

Alternatively, compounds of formula I, can be prepared according to a so called Ullmann reaction by reaction of a compound of the formula XIV, wherein  $L^2$  is a halide, with a compound of the formula  $R^1-H$ , wherein H is a hydrogen on a nitrogen ring atom, in the presence of a suitable base and a suitable catalyst. Suitable bases include alkali metal carbonates or hydroxide bases, preferably potassium carbonate. Suitable catalysts include copper (0) catalyst, preferably finely powdered copper bronze. Suitable solvents for the aforesaid reaction include neat or polar aprotic solvents, such as dimethylformamide (DMF), N,N dimethylacetamide or N-methylpyrrolidinone (NMP). The aforesaid reaction may be run at a temperature between about 80°C and 180°C for about 6 to 24 hours.

Alternatively, compounds of formula I, can be prepared according to a so called Stille coupling by reaction of a compound of the formula XIV, wherein  $L^2$  is a halide or triflate, with a compound of the formula  $R^1-W-SnR_3$ , wherein R is a alkyl and W is a bond,  $-(CH_2)_o-$ ,  $-(CH=CH)-$ ,  $-C\equiv C-$ ,  $-O(CH_2)_o-$ ,  $-O(CH_2)_qO(CH_2)_r-$ ,  $-(CH_2)_rO(CH_2)_r-$ ,  $-NR^7(CH_2)_o-$ ,  $-(CH_2)_rNR^7(CH_2)_r-$ ,  $-O(CH_2)_qNR^7(CH_2)_r-$ ,  $-NR^7(CH_2)_qO(CH_2)_r-$ , and  $-S(O)_nCH_2-$ ; in the presence of a suitable base and a suitable catalyst. If necessary, a salt such as lithium chloride, ammonium hydroxide, copper(I) bromide, may be used. Suitable bases include alkali metal carbonate or hydroxide base, preferably potassium carbonate. Suitable catalysts



include palladium acetate ( $\text{Pd}(\text{OAc})_2$ ), tetrakis(triphenylphosphine)palladium ( $\text{Pd}(\text{PPh}_3)_4$ ) and dichlorobis(triphenylphosphine)palladium. Suitable solvents for the aforesaid reaction include neat or polar aprotic solvents, such as dimethylformamide (DMF), tetrahydrofuran, 1,4-dioxane, benzene, toluene, dimethoxyethane, or N-methylpyrrolidinone (NMP), preferably  
5 tetrahydrofuran and 1,4-dioxane. The aforesaid reaction may be run at a temperature between about 20 to 160 °C, usually 20 to 130 °C for about 10 minutes to 5 days, usually 30 minutes to 15 hours. (See Stille, J.K., Angew. Chem. Int. Ed. Eng., 1986, 25, 508-524).

Alternatively, compounds of formula I, can be prepared according to a so called Stille coupling by reaction of a compound of the formula XIV, wherein  $\text{L}^2$  is  $\text{SnR}_3$ , wherein R is a  
10 alkyl, with a compound of the formula  $\text{R}^1\text{-W}'$  wherein  $\text{W}'$  is a halide, triflate,  $-(\text{C}=\text{O})\text{H}$ ,  $-(\text{C}=\text{O})\text{R}^6$ ,  $-(\text{C}=\text{O})\text{-Cl}$ ,  $-\text{CH}=\text{CH}\text{-(halide)}$ ,  $-\text{O}(\text{CH}_2)_q\text{-O}(\text{CH}_2)_r\text{-(halide)}$ , or  $-(\text{CH}_2)_t\text{O}(\text{CH}_2)\text{-(halide)}$ ; according to methods to those described above for the Stille coupling.

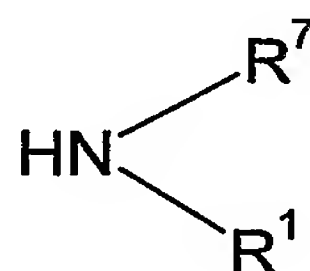
Alternatively, compounds of formula I, can be prepared according to a so called Negishi coupling by reaction of a compound of the formula XIV, wherein  $\text{L}^2$  is a halide or  
15 triflate, with a compound of the formula  $\text{R}^1\text{-W-zinc halide}$ . The catalyst may be selected from those typically employed for the so-called reaction (for example, tetrakis(triphenylphosphine)palladium, tetrakis(triphenylphosphine)nickel, dichlorobis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, / n-BuLi, dichlorobis(1,1-bis(diphenylphosphino)ferrocene)palladium and  
20 dichlorobis(1,4-bis(diphenylphosphino)butane)palladium). Suitable solvents include tetrahydrofuran, diethylether and dimethoxyethane, preferably tetrahydrofuran. The reaction is carried out at a temperature in the range from 20 to 160 °C, usually 20 to 130 °C for 10 minutes to 5 days, usually 30 minutes to 15 hours. Alternatively, one skilled in the art will appreciate that the reactive groups of the reagents can be reversed. Thus, one skilled in the  
25 art will appreciate that  $\text{L}^2$  in the aforesaid reaction can be the zinc halide coupled to an  $\text{R}^1\text{W}'\text{-halide}$  or triflate. (Knochel, P. And Singer, R.D. Chem. Rev., 1993, 93, 2117-2188).

Alternatively, coupling can be carried out by a so called Suzuki coupling reaction of said compound of formula XIV, wherein  $\text{L}^2$  is I, Br, Cl, or triflate, with an  $\text{R}^1\text{-W-borate}$  or  $\text{R}^1\text{-W-boronic acid}$ , a catalyst, a base and a dehydrating agent. Suitable borates include  
30  $(\text{HO})_2\text{B-}$ , 9-BBN, and alkylboranes. Suitable catalysts include copper or palladium, preferably copper (II) acetate or palladium acetate ( $\text{Pd}(\text{OAc})_2$ ), palladium triphenylphosphine or  $\text{Pd}(\text{dppf})\text{Cl}_2$ . Suitable dehydrating agents include 4 angstrom molecular sieves. Suitable bases include tertiary amine bases, such as triethylamine or pyridine,  $\text{Na}_2\text{CO}_3$ , sodium ethoxide, and  $\text{K}_3\text{PO}_4$ . Suitable solvents include methylene chloride, dimethyl sulfoxide  
35 (DMSO) or tetrahydrofuran (THF). The aforesaid reaction is typically performed under an atmosphere of oxygen gas at a temperature of about 10°C to 50°C, preferably about 23°C for

about 6 to 72 hours. Palladium-catalyzed boronic acid couplings are described in Miyaura, N., Yanagi, T., Suzuki, A. Syn. Comm. 1981, 11, 7, p. 513.

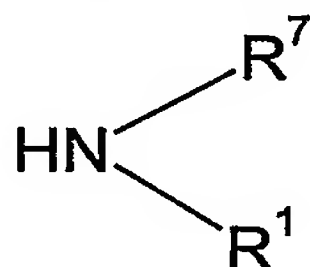
Alternatively, the Suzuki coupling may be carried out in cases where  $L^2$  is  $B(OH)_2$  and  $R^1-W$  is substituted with I, Br, Cl, or triflate or H wherein H is a hydrogen on a nitrogen atom, using a copper or palladium catalyst, preferably copper (II) acetate or palladium acetate using methods analogous to those of the preceding paragraph.

Compounds of formula I wherein W is  $-NR^7-(C=O)-$  can be prepared from compounds of formula XIV, wherein  $L^2$  is  $-CO_2H$  or  $-(C=O)-Cl$ , by reaction with a reagent of the formula



according to standard methods well known to those skilled in the art.

Compounds of formula I wherein W is  $-NR^7SO_2-$  can be prepared from compounds of formula XIV, wherein  $L^2$  is  $-SO_2-Cl$ , by reaction with a reagent of the formula



according to standard methods well known to those skilled in the art.

Alternatively, compounds of formula I can also be prepared from compounds of formula XV or XVI via intermediates of the formula II and XII. The intermediates of the formula II and XII can be converted to compounds of formula I according to the methods of Schemes 1 and 3 respectively. The compounds of formulae II and XII can be prepared from compounds of the formulae XV and XVI, respectively, by coupling reactions analogous to those described above for the conversion of compounds of formula XIV to formula I.

Compounds of the formula XV and XVI are commercially available or can be made by methods well known to those skilled in the art.

Scheme 5 refers to an alternate preparation of compounds of formula I. Referring to Scheme 5, a compound of formula I is prepared from a compound of formula XVII by reduction with tin in the presence of an acid such as hydrochloric acid followed by a so called Sandmeyer reaction wherein a diazonium intermediate is prepared by treatment with sodium nitrite followed by a quench with a cuprous halide such as cuprous chloride or cuprous bromide. Suitable solvents include alcohols such as methanol and ethanol. The aforesaid reaction is conducted at a temperature from about  $-20^\circ C$  to about  $0^\circ C$ , and the reaction is generally run for a period of about 1 to 48 hours.

The compound of formula XVII, wherein  $R^1-W-$  is a standard transformable group, such as  $R^1-O-$ ,  $R^1-(CH_2)_oO-$ ,  $R^1-O(CH_2)_pO-$ ,  $R^1-(CH_2)_rO(CH_2)_qO-$ ,  $R^1-(NR^7)-$ ,  $R^1-(CH_2)_oNR^7-$ ,  $R^1-O(CH_2)_pNR^7-$ ,  $R^1-(CH_2)_rNR^7(CH_2)_qO-$ ,  $R^1-NR^7(CH_2)_qO-$ ,  $R^1-CONR^7-$ ,  $R^1-S-$ ,  $R^1-CH_2S-$ ; or W is a bond and  $R^1$  is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring containing an NH can be prepared from a compound of the formula XVIII by reaction with a nucleophile according to standard chemical methods well known to those skilled in the art. Methods for nucleophilic aromatic substitution are reviewed in Belfield *et al.*, Tetrahedron, 55, 11399-11428 (1999), in March, Advanced Organic Chemistry, 641-676 (John Wiley & Sons, Inc., Fourth Edition, 1992).

Compounds of formula XVIII are commercially available or can be made by methods known to those skilled in the art.

Alternatively, compounds of formula I and II can be prepared from compounds of formula XX by analogous Sandmeyer methods as described above.

Compounds of formula XX can be prepared from compounds of formula XXI by methods analogous to the conversion of compounds of formula XVIII to XVII described above.

Compounds of formula XXI are commercially available or can be made by methods well known to those skilled in the art.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, e.g., where  $R^4$  includes a 6-azauracil or barbituric acid moiety, are capable of forming base salts with various

pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

The activity of the compounds of the invention for the various disorders described above can be determined according to one or more of the following assays. All of the compounds of the invention, that were tested, had an  $IC_{50}$  of less than 1  $\mu M$  in the *in vitro* human monocyte assay described below.

#### PHARMACOLOGICAL ANALYSIS

Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the  $P2X_7$  receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p. 126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. Alternatively, the propidium dye YOPRO-1 can be substituted for ethidium bromide so as to detect uptake of the dye. The increase in fluorescence can be used as a measure of  $P2X_7$  receptor activation and therefore to quantify the effect of a compound on the  $P2X_7$  receptor.

In this manner, the compounds of the invention can be tested for antagonist activity at the  $P2X_7$  receptor. 96-Well flat bottomed microtitre plates are filled with 250  $\mu l$  of test solution comprising 200  $\mu l$  of a suspension of THP-1 cells ( $2.5 \times 10^6$  cells/ml, more preferably prestimulated as described in the literature with a combination of LPS and TNF to promote receptor expression) containing  $10^{-4} M$  ethidium bromide, 25  $\mu l$  of a high potassium, low sodium buffer solution (10mM Hepes, 150 mM KCl, 5 mM D-glucose and 1.0% FBS at pH 7.5) containing  $10^{-5} M$  bbATM, and 25  $\mu l$  of the high potassium buffer solution containing  $3 \times 10^{-5} M$  test compound (more preferably  $5 \times 10^{-4} M$ , more preferably  $1 \times 10^{-4} M$ , more preferably  $1 \times 10^{-3} M$ ). The plate is covered with a plastic sheet and incubated at  $37^\circ C$  for one hour. The



plate is then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X<sub>7</sub> receptor agonist) and pyridoxal 5-phosphate (a P2X<sub>7</sub> receptor antagonist) can be used separately in the test as controls. From the readings obtained, a pIC<sub>50</sub> figure can be  
5 calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%.

In like manner, the compounds of the invention can be tested for antagonist activity at the P2X<sub>7</sub> receptor using the cytokine IL-1  $\beta$  as the readout. Blood collected from normal volunteers in the presence of heparin is fractionated using lymphocyte separation medium  
10 obtained from Organon Technica (Westchester, PA). The region of the resulting gradient containing banded mononuclear cells is harvested, diluted with 10 ml of Maintenance Medium (RPMI 1640, 5% FBS, 25 mM Hepes, pH 7.2, 1% penicillin/streptomycin), and cells are collected by centrifugation. The resulting cell pellet was suspended in 10 ml of Maintenance Medium and a cell count was performed. In an average experiment,  $2 \times 10^5$  mononuclear  
15 cells are seeded into each well of 96-well plates in a total volume of 0.1 ml. Monocytes are allowed to adhere for 2 hours, after which the supernatants are discarded and the attached cells are rinsed twice and then incubated in Maintenance Medium overnight at 37°C in a 5% CO<sub>2</sub> environment.

The cultured monocytes can be activated with 10 ng/ml LPS (E. coli serotype 055:B5; Sigma Chemicals, St. Louis, MO). Following a 2-hour incubation, the activation medium is removed, the cells are rinsed twice with 0.1 ml of Chase Medium (RPMI 1640, 1% FBS, 20 mM Hepes, 5 mM NaHCO<sub>3</sub>, pH 6.9), and then 0.1 ml of Chase Medium containing a test agent is added and the plate is incubated for 30 minutes; each test agent concentration can be evaluated in triplicate wells. ATP then is introduced (from a 100 mM stock solution, pH 7)  
25 to achieve a final concentration of 2 mM and the plate is incubated at 37°C for an additional 3 hours. Media were harvested and clarified by centrifugation, and their IL-1 $\beta$  content was determined by ELISA (R&D Systems; Minneapolis, MN).

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active  
30 compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous), topical or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica);  
35



disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula I can also be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397, which are herein incorporated by reference in their entirety.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution, dry powder formulation or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, heptafluoroalkanes, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (inflammation) is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

5           The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from  
10   0.05 to 99% w (per cent by weight), more preferably from 0.10 to 70% w, of active ingredient, and, from 1 to 99.95% w, more preferably from 30 to 99.90% w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Aerosol formulations for treatment of the conditions referred to above in the average  
15   adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 $\mu$ g to 1000 $\mu$ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 $\mu$ g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

Aerosol combination formulations for treatment of the conditions referred to above  
20   (e.g., adult respiratory distress syndrome) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 1  $\mu$ g to 1000  $\mu$ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100  $\mu$ g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

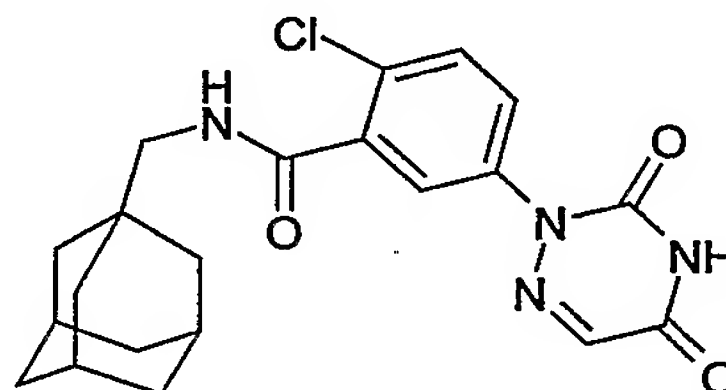
Aerosol formulations for treatment of the conditions referred to above (e.g., adult  
25   respiratory distress syndrome) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 20  $\mu$ g to 1000  $\mu$ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100  $\mu$ g to 10 mg of the p38 kinase inhibitor. Administration may be several times daily, for  
30   example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

This invention also encompasses pharmaceutical compositions containing and methods of treating or preventing comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a  
35   polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino

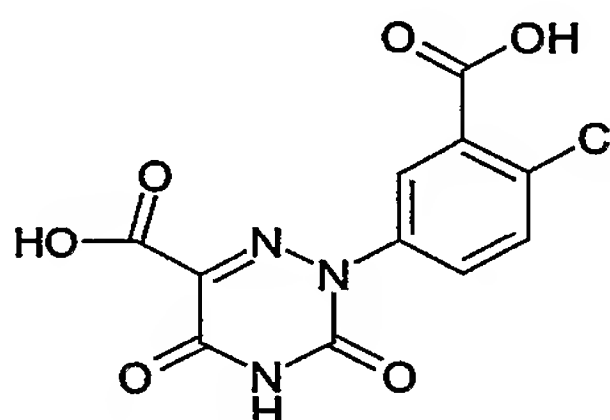
acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (d) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Mass Spectral data were obtained using a Micromass ZMD APCI Mass Spectrometer equipped with a Gilson gradient high performance liquid chromatograph. The following solvents and gradients were used for the analysis. Solvent A; 98% water/2% acetonitrile/0.01% formic acid and solvent B; acetonitrile containing 0.005% formic acid. Typically, a gradient was run over a period of about 4 minutes starting at 95% solvent A and ending with 100% solvent B. The mass spectrum of the major eluting component was then obtained in positive or negative ion mode scanning a molecular weight range from 165 AMU to 1100 AMU. Specific rotations were measured at room temperature using the sodium D line (589 nm). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

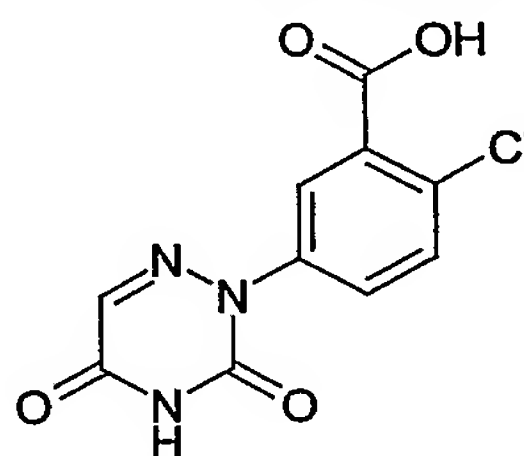
One of ordinary skill in the art will appreciate that in some cases protecting groups may be required during preparation. After the target molecule is made, the protecting group can be removed by methods well known to those of ordinary skill in the art, such as described in Greene and Wuts, "Protective Groups in Organic Synthesis" (2<sup>nd</sup> Ed, John Wiley & Sons 1991).

**EXAMPLE 1****N-ADAMANTAN-1-YLMETHYL-2-CHLORO-5-(3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]TRIAZIN-2-YL)-BENZAMIDE**

5           **A:**       2-(3-Carboxy-4-chloro-phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazine-6-carboxylic acid



To a mechanically stirred solution of 5-amino-2-chloro-benzoic acid methyl ester (5.0 g, 26.9 mmol) in glacial acetic acid (100 ml) was added 12 N hydrochloric acid (7.5 ml). After 30 minutes at room temperature the reaction mixture was cooled to 10°C and a solution of NaNO<sub>2</sub> in water (5 ml) was added dropwise at a rate that kept the reaction temperature between 10° and 15°C. During this time it was observed that the reaction went from purple to light brown. After stirring for 30 minutes at 10°C sodium acetate (5.4 g) followed by (3-ethoxycarbonylamino-3-oxo-propionyl)-carbamic acid ethyl ester (7.2 g) were added at once. After stirring for 20 minutes at 10°C followed by 1 hour at room temperature an additional 2.2 g of sodium acetate was added. After stirring at reflux for 6 hours the reaction mixture was cooled to room temperature and 50% aqueous sulfuric acid (29 ml) was added. After stirring the resulting mixture at reflux for 2 hours the mixture was cooled to room temperature, diluted with water (135 ml) and filtered. The precipitate was washed with water and dried under vacuum. The crude solid was recrystallized from isopropyl ether to give 3.8 g (46%) of the title intermediate as an orange solid. Mass spec [M-1] 3:1 ratio of 310.1 and 312.1; <sup>1</sup>H nmr (500 MHz, CD<sub>3</sub>OD) δ 7.64 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 2.6 Hz, 1H).

**B: 2-Chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid**

A suspension of 2-(3-carboxy-4-chloro-phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]-triazine-6-carboxylic acid (3.4 g) in mercaptoacetic acid (2 ml) was stirred at 175°C. After 20 hours the resulting solution was cooled to room temperature during which time a precipitate formed. The mixture was dumped into ice-water, stirred for 30 minutes and filtered to give a yellow solid. The solid was dried under vacuum for 24 hours to give 2.1 g of the title intermediate. Mass spec [M-1] 3:1 ratio of 266.1 and 268.1; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.58 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.72 (dd, J = 2.6 and 8.8 Hz), 8.09 (d, J = 2.6 Hz).

**C: N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide**

To a stirred solution of 2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid (48 mg, 0.18 mmol), EDCI (67 mg) and HOBT (47 mg) in DMF (1.5 ml) was added a solution of 1-adamantane methylamine (36 mg) in DMF (0.5 ml). After 20 minutes triethylamine (49 µl) was added. After 18 hours the reaction mixture was diluted with dichloromethane (75 ml) and washed sequentially with water, 1N HCl and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to give 73 mg of an amorphous solid. The solid was purified by silica gel chromatography eluting with 1:1 ethylacetate/hexanes to give 22 mg of the title compound, as a white amorphous solid. Mass spec [M-1] 3:1 ratio of 413.5 and 415.5; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 1.61 (s, 6H), 1.68 (d, J = 11.6 Hz, 3H), 1.75 (d, J = 12.5 Hz, 3H), 1.97 (s, 3H), 3.05 (s, 2H), 7.54 - 7.56 (m, 2H), 7.61 - 7.65 (m, 2H), 8.54 (broad t, 1H).

**Examples 2-3** are presented in **Table 1** and were prepared analogously to the synthesis outlined in **Example 1C**, coupling the appropriate amine to 2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid. Final products were analyzed by LC/MS using a Micromass ZMD LC/MS (ESI mode). The method used for the HPLC mobile phase gradient change was as follows:

	<u>Time (min)</u>	<u>A%</u>	<u>B%</u>
	0.00	95	5
30	1.0	80	20
	2.3	50	50
	3.7	0	100
	3.7	95	5

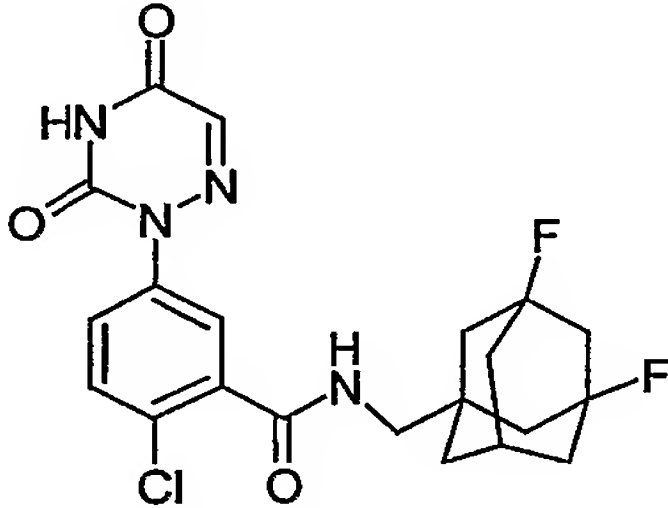
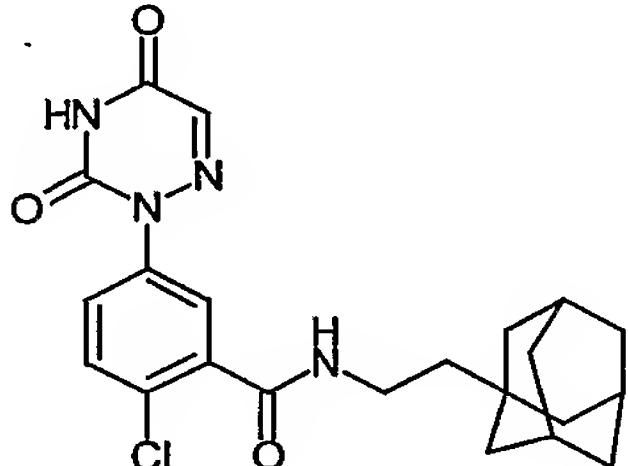


Solvent A= 98% Water + 2% Acetonitrile + 0.01% Formic Acid

Solvent B = Acetonitrile + 0.005% Formic Acid

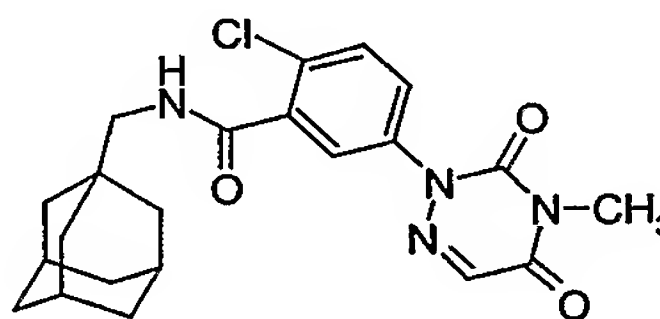
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**TABLE 1**

Ex.	Structure	Mass Spectra (ES+)	Mass Spectra (ES-)	LC Retention Time (min)
2		452.0	450.0	2.4
3		--	427.3	2.8

**EXAMPLE 4****N-ADAMANTAN-1-YLMETHYL-2-CHLORO-5-(4-METHYL-3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]TRIAZIN-2-YL)-BENZAMIDE**

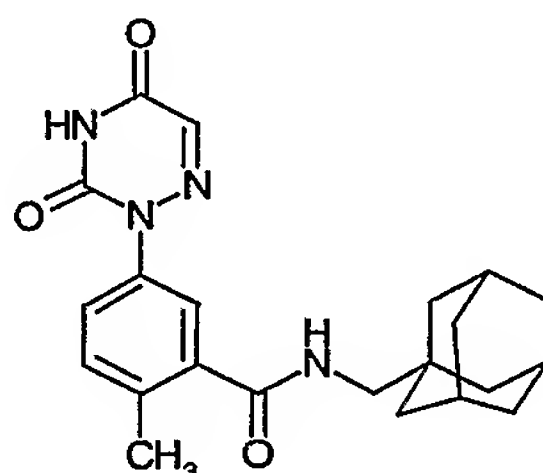
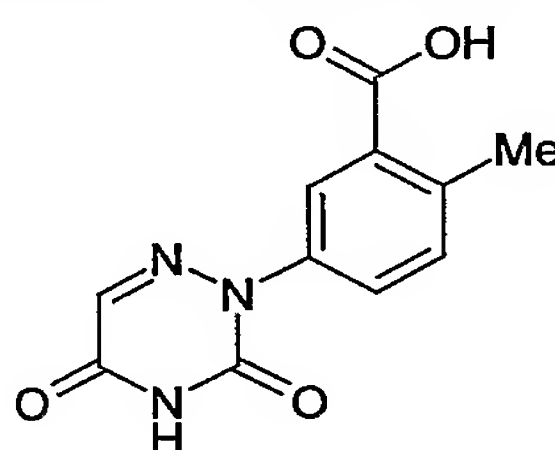
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To a stirred solution of N-adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide (66 mg, 0.159 mmol) in dioxane (1.5 ml) was added methanol (0.32 ml) followed by a 2.0 M solution of (trimethylsilyl)diazomethane (0.32 ml). After stirring for 18 hours at ambient temperature the mixture was concentrated under reduced pressure to give 67 mg of a light yellow amorphous solid. Mass Specrum (ES+) 429.6; (ES-) 427.6. Liquid chromatography retention time = 2.8 min (using the LC/MS and method outlined for the examples in Table 1).

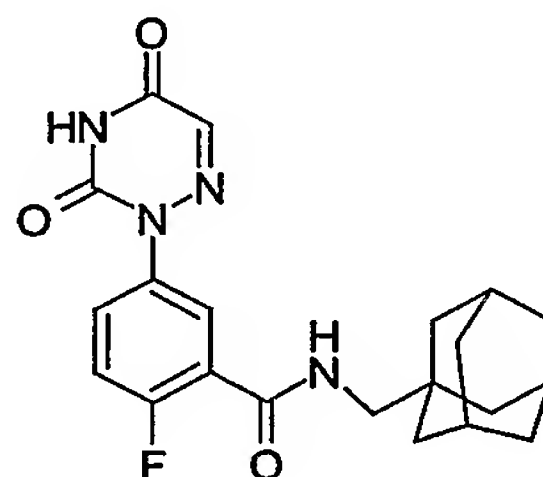


**EXAMPLE 5****N-ADAMANTAN-1-YLMETHYL-5-(3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]TRIAZIN-2-YL)-2-METHYL-BENZAMIDE****5      A: 2-Methyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid**

5-Amino-2-chloro-benzoic acid methyl ester (3.5 g, 21.2 mmol) was dissolved in glacial acetic acid (80 ml) and 5.5 ml of concentrated HCl was added. After stirring with an overhead stirrer for 30 minutes at ambient temperature the mixture was cooled to 10°C and a solution of NaNO<sub>2</sub> (1.6 g) in water (4 ml) was added dropwise, keeping the internal temperature below 15°C. During this addition the reaction mixture changed from amber to a cloudy orange. After 30 minutes sodium acetate (3.8 g, 46.6 mmol) and (3-ethoxycarbonylamino-3-oxo-propionyl)-carbamic acid ethyl ester (5.7 g, 23.3 mmol) were added at once. After 10 minutes the reaction was warmed to ambient temperature. After 1 hour additional sodium acetate (1.7 g, 21.2 mmol) was added and the reaction mixture was heated at reflux. After 3 hours the deep red-brown mixture was treated with 50% sulfuric acid (23 ml) and heated again at reflux. After 2 hours the mixture was concentrated under reduced pressure and then water (200 ml) was added. After stirring for 30 minutes the gold precipitate (3.5 g) was collected by filtration. The resulting solid was suspended in 3 ml of mercaptoacetic acid and stirred at 175°C. After 4 hours the mixture was allowed to cool and sit for 16 hours. The mixture was diluted with water (100 ml) and stirred for 1 hour. The resulting brown solid (2.1 g) was collected by filtration. Mass spectrum [M-1] 246.4.

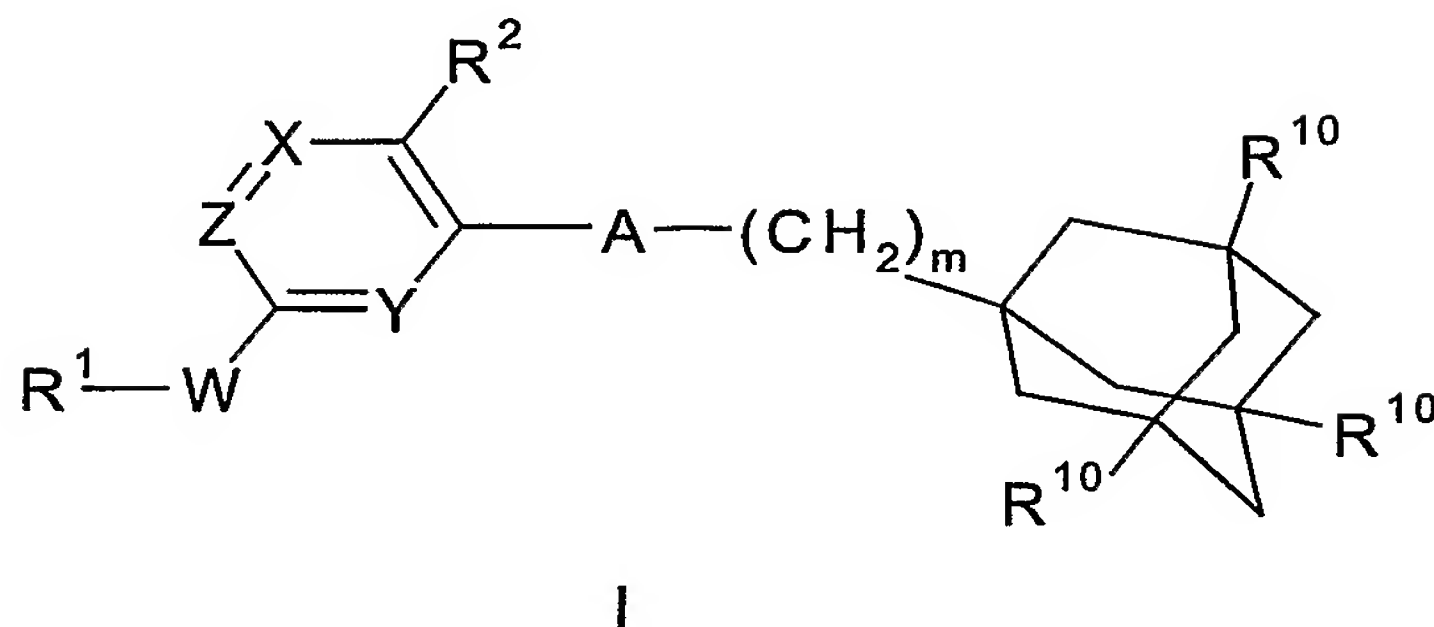
**B: N-[2-(2-Chloro-phenyl)-ethyl]-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-methyl-benzamide**

25      The title compound was prepared using the method outlined in **Example 1C**, coupling 2-methyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid with 1-adamantane methylamine. The product was a colorless oil. MS (ES+) 395.6; (ES-) 393.5; LC retention time = 2.5 min (using the LC/MS and method outlined for the examples in Table 1).

**EXAMPLE 6****N-ADAMANTAN-1-YLMETHYL-5-(3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]TRIAZIN-2-YL)-2-FLUORO-BENZAMIDE**

CLAIMS

1. A compound of the formula



wherein A is  $-(C=O)NH-$  or  $-NH(C=O)-$ ;

5 X, Y and Z are  $=(CR^3)-$ ,  $=(CR^4)-$ , and  $=(CR^5)-$ ; or  $=N-$ ,  $=(CR^4)-$ , and  $=(CR^5)-$ ; or  $=(CR^3)-$ ,  $=N-$ , and  $=(CR^5)-$ ; or  $=(CR^3)-$ ,  $=(CR^4)-$ , and  $=N-$ ; or  $=N-$ ,  $=(CR^4)-$ , and  $=N-$ ; or  $=(CR^3)-$ ,  $=N-$ , and  $=N-$ ; or  $=N-$ ,  $=N-$ , and  $CR^5$ , respectively;

W is a bond,  $-O-$ ,  $>(C=O)$ ,  $-(CH_2)_o-$ ,  $-(CH=CH)-$ ,  $-C\equiv C-$ ,  $-(CH_2)_oO-$ ,  $-O(CH_2)_o-$ ,  
 10  $-O(CH_2)_pO-$ ,  $-O(CH_2)_qO(CH_2)_r-$ ,  $-CR^6(OH)-$ ,  $-(CH_2)_rO(CH_2)_r-$ ,  $-(CH_2)_rO(CH_2)_qO$ ,  $>NR^7$ ,  
 $-(CH_2)_oNR^7-$ ,  $-NR^7(CH_2)_o-$ ,  $-(CH_2)_rNR^7(CH_2)_r-$ ,  $-O(CH_2)_pNR^7-$ ,  $-O(CH_2)_qNR^7(CH_2)_r-$ ,  
 $-(CH_2)_rNR^7(CH_2)_qO-$ ,  $-NR^7(CH_2)_qO-$ ,  $-NR^7(CH_2)_qO(CH_2)_r-$ ,  $-CONR^7-$ ,  $-NR^7CO-$ ,  $>S(O)_n$ ,  
 $-S(O)_nCH_2-$ ,  $-CH_2S(O)_n-$ ,  $-SO_2NR^7-$ , or  $-NR^7SO_2-$ ;

m is an integer from 1 to 2;

n is an integer from 0 to 2;

15 o is an integer from 1 to 6;

p is an integer from 2 to 6;

q is an integer from 2 to 3;

r is an integer from 1 to 3;

20  $R^1$  is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring containing three to five nitrogen atoms and zero to three additional heteroatoms independently selected from the group consisting of  $-O-$  and  $-S(O)_n$ ; wherein any of said carbon atoms of said 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring may optionally contain 1-3 oxo groups; wherein one to three of said nitrogen atoms of said heterocycle able to support an additional substituent may also optionally be substituted by  $R^8$ ; wherein any carbon atom of said heterocycle able to support an additional substituent may also optionally be substituted by one to four  $R^9$  substituents per ring;

$R^2$  is selected from the group consisting of (i) hydrogen, (ii) halogen, (iii) cyano, (iv)  $(C_1-C_4)$ alkyl optionally substituted by one to four chloro or fluoro, (v)  $(C_2-C_4)$ alkenyl; (vi)  $(C_2-C_4)$ alkynyl and (vii)  $(C_1-C_4)$ alkyloxy optionally substituted by one to four chloro or fluoro;

30  $R^3$ ,  $R^4$  and  $R^5$  are each independently selected from the group consisting of (i) hydrogen; (ii) halogen, (iii) cyano, (iv) nitro, (v) amino, (vi) hydroxyl, (vii)  $(C_1-C_6)$ alkyl optionally

substituted by one to four chloro or fluoro, (viii) (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl optionally substituted by one to four chloro or fluoro, (ix) (C<sub>1</sub>-C<sub>6</sub>)alkyloxy optionally substituted by one to four chloro or fluoro, and (x) (C<sub>3</sub>-C<sub>8</sub>)cycloalkyloxy optionally substituted by one to four chloro or fluoro;

R<sup>6</sup> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

5 R<sup>7</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl;

R<sup>8</sup> is absent or is selected from the group consisting of hydrogen, -CF<sub>3</sub>, (C<sub>1</sub>-C<sub>6</sub>)alkyl, HO-(C<sub>2</sub>-C<sub>6</sub>)alkyl and (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl,

10 R<sup>9</sup> is selected from the group suitable substituents such as hydrogen, halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with one to six fluoro, -CO<sub>2</sub>H, HO-(C<sub>2</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with one to six fluoro, hydroxy, (C<sub>1</sub>-C<sub>10</sub>)heteroaryl and (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl,

each R<sup>10</sup> is independently selected from the group consisting of hydrogen or halo; or a pharmaceutically acceptable salt or solvate thereof.

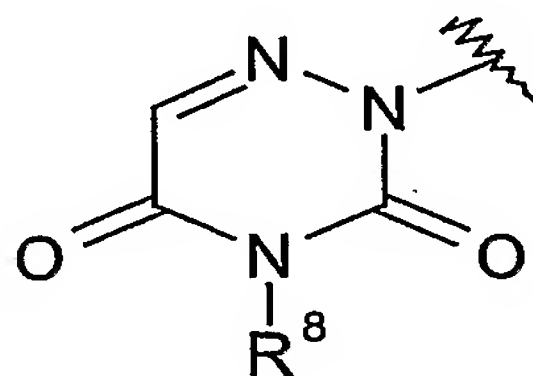
15 2. A compound according to claim 1 wherein X, Y and Z are =(CR<sup>3</sup>)-, =(CR<sup>4</sup>)-, and =(CR<sup>5</sup>)-; respectively.

3. A compound according to any of the previous claims wherein one of R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> is selected from the group consisting of (i) hydrogen (ii) halogen, (ii) cyano, (iii) nitro, (iv) amino, (v) hydroxyl, (vi) (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by one to four chloro or fluoro, (vii) (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl optionally substituted by one to four chloro or fluoro, (viii) (C<sub>1</sub>-C<sub>6</sub>)alkyloxy optionally substituted by one to four chloro or fluoro, and (ix) (C<sub>3</sub>-C<sub>8</sub>)cycloalkyloxy optionally substituted by one to four chloro or fluoro.

4. A compound according to any of the previous claims wherein m is one.

5. A compound according to any of the previous claims wherein A is -(C=O)NH-.

6. A compound according to claims 1 to 13 wherein R<sup>1</sup> is

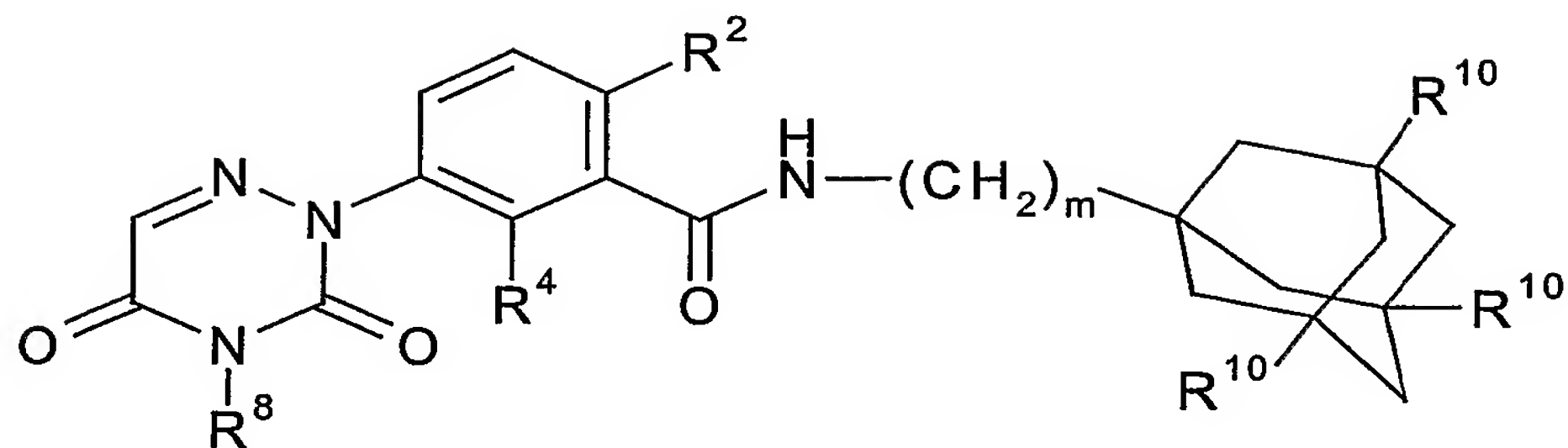


25

wherein R<sup>8</sup> is selected from the group consisting of hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl.

7. A compound according to any of the previous claims wherein W is a bond.

8. A compound according to claim 1 wherein said compound of formula I has the formula



1a

wherein m is an integer from 1 to 2;

$R^2$  is fluoro or chloro;

$R^4$  is selected from the group consisting of hydrogen, halogen, cyano, hydroxyl,  
 5 (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>3</sub>)alkyloxy, -CF<sub>3</sub>, -OCF<sub>3</sub> and (C<sub>3</sub>-C<sub>6</sub>)cycloalkyloxy;

$R^8$  is a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl, CF<sub>3</sub>-CH<sub>2</sub>-, HO-(C<sub>2</sub>-C<sub>6</sub>)alkyl or  
 (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl group;

$R^{10}$  is hydrogen or fluoro;

or a pharmaceutically acceptable salt or solvate thereof.

10 9. A method of treating a P2X<sub>7</sub> mediated disease in a mammal in need thereof,  
 which comprises administering to said mammal an effective amount of a compound according  
 to any of the previous claims.

10 10. A pharmaceutical composition for the treatment of a P2X<sub>7</sub> mediated disease  
 in a mammal which comprises an effective amount of a compound according to any of the  
 15 previous claims and a pharmaceutically acceptable carrier.



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 02/04043

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D253/06 C07C13/615 A61P37/00 A61P11/06 A61P29/00  
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 01 094338 A (ASTRAZENECA AB, SWED.) 13 December 2001 (2001-12-13) the whole document ---	1-10
X	WO 00 061569 A (ASTRAZENECA AB, SWED.) 19 October 2000 (2000-10-19) cited in the application the whole document ---	1-10
X	WO 99 29660 A (ASTRA PHARMACEUTICALS LTD., UK; ASTRA AKTIEBOLAG) 17 June 1999 (1999-06-17) cited in the application the whole document ---	1-10

-/-

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

29 November 2002

Date of mailing of the international search report

10/12/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Schuemaker, A

## INTERNATIONAL SEARCH REPORT

In ☐ International Application No

PCT/IB 02/04043

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NARAYANAN V L: "ADAMANTYL ANALOGS OF 2'-(DIMETHYLAMINOPROPYLTHIO)CINNAMANILIDE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 15, no. 11, 1972, pages 1180-1182, XP002938144 ISSN: 0022-2623 the whole document ----	1-10
Y	WO 01 044213 A (ASTRAZENECA AB, SWED.) 21 June 2001 (2001-06-21) cited in the application claim 1; example 53 ----	1-10
A	US 3 789 072 A (BERNSTEIN J) 29 January 1974 (1974-01-29) claim 1 -----	1-8

# INTERNATIONAL SEARCH REPORT

national application No.  
PCT/IB 02/04043

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

al Application No  
PCT/IB 02/04043

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